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Patentanmeldung Nr. Patent application No. Demande de brevet n°

02292077.1

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151 85 Södertälje
SUEDE

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(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se référer à la description.)

Chemical compounds

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- 1 -

CHEMICAL COMPOUNDS

The present invention relates to compounds which are antagonists of gonadotropin releasing hormone (GnRH) activity. The invention also relates to pharmaceutical formulations, the use of a compound of the present invention in the manufacture of a medicament, a method of therapeutic treatment using such a compound and processes for producing the compounds.

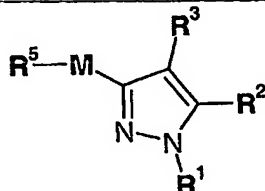
Gonadotropin releasing hormone (GnRH) is a decapeptide that is secreted by the hypothalamus into the hypophyseal portal circulation in response to neural and/or chemical stimuli, causing the biosynthesis and release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) by the pituitary. GnRH is also known by other names, including gonadoliberin, LH releasing hormone (LHRH), FSH releasing hormone (FSH RH) and LH/FSH releasing factor (LH/FSH RF).

GnRH plays an important role in regulating the action of LH and FSH (by regulation of their levels), and thus has a role in regulating the levels of gonadal steroids in both sexes, including the sex hormones progesterone, oestrogens and androgens. More discussion of GnRH can be found in WO 98/5519 and WO 97/14697, the disclosures of which are incorporated herein by reference.

It is believed that several diseases would benefit from the regulation of GnRH activity, in particular by antagonising such activity. These include sex hormone related conditions such as sex hormone dependent cancer, benign prostatic hypertrophy and myoma of the uterus. Examples of sex hormone dependent cancers are prostatic cancer, uterine cancer, breast cancer and pituitary gonadotrophe adenoma.

The following disclose compounds purported to act as GnRH antagonists:
WO 97/21435, WO 97/21703, WO 97/21704, WO 97/21707, WO 55116, WO 98/55119, WO 98/55123, WO 98/55470, WO 98/55479, WO 99/21553, WO 99/21557, WO 99/41251, WO 99/41252, WO 00/04013, WO 00/69433, WO 99/51231, WO 99/51232, WO 99/51233, WO 99/51234, WO 99/51595, WO 99/51596, WO 00/53178, WO 00/53180, WO 00/53179, WO 00/53181, WO 00/53185 and WO 00/53602.

It would be desirable to provide further compounds, such compounds being GnRH antagonists. Thus, according to the first aspect of the invention there is provided a compound of Formula (I),

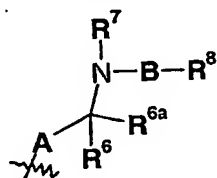


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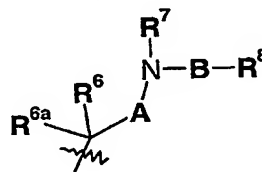
Formula (I)

wherein:

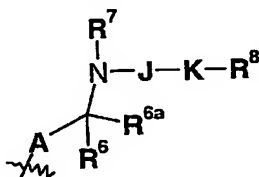
- R^1 is selected from: hydrogen, optionally-substituted C_{1-6} alkyl, optionally substituted aryl or optionally-substituted aryl C_{1-6} alkyl;
- 10 R^2 is an optionally-substituted mono or bi-cyclic aromatic ring;
- R^3 is selected from a group of Formula (IIa) to Formula (IIf):



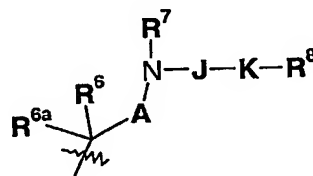
Formula (IIa)



Formula (IIb)

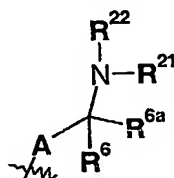


Formula (IIc)

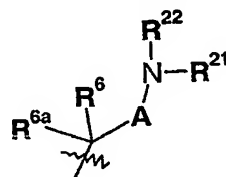


Formula (IId)

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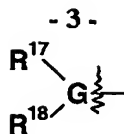


Formula (IIe)



Formula (IIf)

- R^4 is selected from: hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted aryl, C_{1-3} perfluoroalkyl, cyano, nitro, halo, $R^9O(CH_2)_m$ -, $R^9C(O)N(R^{10})$ -,
- 20 $R^9R^{10}NC(O)N(R^{10})$ - or $R^9S(O)_n$ -;
- R^5 is a group of Formula (III):



Formula (III)

R^6 and R^{6a} are independently selected from hydrogen, optionally substituted C_{1-6} alkyl, optionally-substituted aryl or optionally substituted aryl C_{1-6} alkyl, or R^6 and R^{6a} taken together and the carbon atom to which they are attached form a carbocyclic ring of 3-7 atoms, or R^6 and R^{6a} taken together and the carbon atom to which they are attached form a carbonyl group;

or when A is not a direct bond the group forms a carbocyclic ring of 3-7 carbon atoms or a heterocyclic ring containing one or more heteroatoms;

or the group forms a heterocyclic ring containing 3-7 carbon atoms and one or more heteroatoms;

R^7 is selected from: hydrogen, optionally-substituted C_{1-6} alkyl, optionally-substituted aryl C_{1-6} alkyl, optionally-substituted aryl, optionally substituted heterocyclyl, optionally substituted heterocyclyl C_{1-6} alkyl, R^9OC_{1-6} alkyl-, $R^9R^{10}NC_{1-6}$ alkyl-, $R^9R^{10}NC(O)C_{1-6}$ alkyl, $-C(NR^9R^{10})=NH$;

or when R^3 is a group of Formula (Iic) or (Iid) R^7 is of the formula $-J-K-R^8$;

R^8 is selected from:

- (i) hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo C_{1-6} alkyl, C_{1-4} alkoxy C_{1-4} alkyl, hydroxy, hydroxy C_{1-6} alkyl, cyano, N- C_{1-4} alkylamino, N,N-di- C_{1-4} alkylamino, C_{1-6} alkyl- $S(O)_n$ -, $-O-R^b$, $-NR^bR^c$, $-C(O)-R^b$, $-C(O)O-R^b$, $-CONR^bR^c$ or $NH-C(O)-R^b$, where R^b and R^c are independently selected from hydrogen and C_{1-4} alkyl optionally substituted with hydroxy, amino, N- C_{1-4} alkylamino, N,N-di- C_{1-4} alkylamino, HO- C_{2-4} alkyl-NH- or HO- C_{2-4} alkyl-N(C_{1-4} alkyl)-;
- (ii) nitro when B is a group of Formula (IV) and X is CH and p is 0;
- (iii) C_{3-7} cycloalkyl, aryl or aryl C_{1-6} alkyl each of which is optionally substituted by R^{12} , R^{13} and R^{14} ;

(iv) $-(Q)\text{-aryl}$, $-(Q)\text{-heterocyclyl}$, -aryl-(Q)-aryl , each of which is optionally substituted by R^{12} , R^{13} and R^{14}
wherein $-(Q)\text{-}$ is selected from E, F or a direct bond;

(v) heterocyclyl or heterocyclyl C_{1-6} alkyl each of which is optionally substituted by R^{12} , R^{13} and R^{14} ;

(vi) a group selected from R^{12} , R^{13} and R^{14} ;

R^9 and R^{10} are independently selected from: hydrogen, hydroxy, optionally substituted C_{1-6} alkyl, optionally substituted aryl, optionally substituted aryl C_{1-6} alkyl, an optionally substituted carbocyclic ring of 3-7 atoms, optionally substituted heterocyclyl, optionally substituted heterocyclyl C_{1-6} alkyl or R^9 and R^{10} taken together can form an optionally substituted ring of 3-9 atoms or R^9 and R^{10} taken together with the carbon atom to which they are attached form a carbonyl group;

R^{11} is selected from: hydrogen, optionally substituted C_{1-6} alkyl, or $N(R^9R^{10})$;

R^{12} is selected from: hydrogen, hydroxy, $R^{17}R^{18}N\text{-}$, optionally substituted

C_{1-6} alkyl- $SO_2N(R^9)\text{-}$, optionally substituted aryl- $SO_2N(R^9)\text{-}$,

C_{1-3} perfluoroalkyl- $SO_2N(R^9)\text{-}$; optionally substituted C_{1-6} alkyl- $N(R^9)SO_2\text{-}$, optionally substituted aryl- $N(R^9)SO_2\text{-}$, C_{1-3} perfluoroalkyl- $N(R^9)SO_2\text{-}$ optionally substituted

C_{1-6} alkanoyl- $N(R^9)SO_2\text{-}$; optionally substituted aryl- $C(O)N(R^9)SO_2\text{-}$, optionally substituted C_{1-6} alkyl- $S(O_n)\text{-}$, optionally substituted aryl- $S(O_n)\text{-}$, C_{1-3} perfluoroalkyl-

C_{1-3} perfluoroalkoxy, optionally substituted C_{1-6} alkoxy, carboxy, halo, nitro or cyano;

R^{13} and R^{14} are independently selected from: hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, cyano, nitro, C_{1-3} perfluoroalkyl-

C_{1-3} perfluoroalkoxy, optionally substituted aryl, optionally substituted aryl C_{1-6} alkyl,

$R^9O(CH_2)_s\text{-}$, $R^9(O)O(CH_2)_s\text{-}$, $R^9OC(O)(CH_2)_s\text{-}$, $R^{16}S(O_n)(CH_2)_s\text{-}$, $R^9R^{10}NC(O)(CH_2)_s\text{-}$

or halo;

R^{15} is selected from: hydrogen, optionally substituted C_{1-6} alkyl, $R^{19}OC(O)\text{-}$,

$R^9R^{10}NC(O)\text{-}$, $R^9C(O)\text{-}$, $R^9S(O_n)\text{-}$;

R^{16} is selected from: hydrogen, C_{1-6} alkyl, C_{1-3} perfluoroalkyl or optionally-substituted aryl;

R^{17} is independently selected from: hydrogen, hydroxy, cyano or optionally substituted

C_{1-6} alkyl;

R^{18} is a group of formula $R^{18a}\text{-C}(R^9R^{10})_{0-1}\text{-}$ wherein R^{18a} is selected from: $R^{19}OC(O)\text{-}$,

$R^9R^{10}NC(O)\text{-}$, $R^9R^{10}N\text{-}$, $R^9C(O)\text{-}$, $R^9C(O)N(R^{10})\text{-}$, $R^9R^{10}NC(O)\text{-}$, $R^9R^{10}NC(O)N(R^{10})\text{-}$,

$R^9SO_2N(R^{10})\text{-}$, $R^9R^{10}NSO_2N(R^{10})\text{-}$, $R^9C(O)O\text{-}$, $R^9OC(O)\text{-}$, $R^9R^{10}NC(O)O\text{-}$, $R^9O\text{-}$,

$R^9S(O_n)-$, $R^9R^{10}NS(O_n)-$, optionally substituted C_{1-6} alkyl, optionally substituted heterocyclyl;

or R^{17} and R^{18} when taken together form an optionally substituted carbocyclic ring of 3-7 atoms or optionally substituted heterocyclyl;

- 5 R^{19} is selected from: hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted aryl, optionally substituted aryl C_{1-6} alkyl, optionally substituted C_{3-7} cycloalkyl, optionally substituted heterocyclyl or optionally substituted heterocyclyl C_{1-6} alkyl;

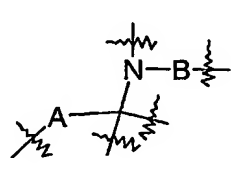
R^{20} is selected from R^{12} or R^{13} ;

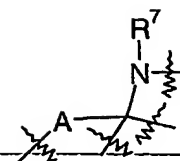
- 10 R^{21} and R^{22} are independently selected from hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-7} cycloalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclyl C_{1-6} alkyl, optionally substituted C_{3-6} alkenyl, optionally substituted C_{3-6} alkynyl, $-(C_{1-5}alkyl)_{aa}-S(O_n)-(C_{1-5}alkyl)_{bb}-$; $R^9R^{10}NC_{2-6}alkyl$, $R^9OC_{2-6}alkyl$ or $R^9R^{10}NC(O)C_{2-6}alkyl$, with the proviso that R^9 and R^{10} independently or taken together are not optionally substituted aryl or optionally substituted aryl C_{1-6} alkyl; or

R^{21} and R^{22} taken together form an optionally substituted non-aromatic heterocyclic ring;

A is selected from:

- (i) a direct bond;
- (ii) optionally-substituted C_{1-5} alkylene wherein the optional substituents are
- 20 independently selected from: optionally-substituted C_{1-6} alkyl, optionally-substituted aryl, optionally substituted aryl C_{1-6} alkyl or substituted aryl C_{1-6} alkyl;
- (iii) a carbocyclic ring of 3-7 atoms;
- (iv) a carbonyl group;

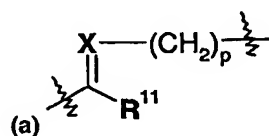
- 25 or when R^3 is a group of Formula (IIa) or (IIb), the group  forms a heterocyclic ring containing 3-7 carbon atoms and one or more heteroatoms;



or when R^3 is a group of Formula (IIa), (IIb), (IIc) or (IId), the group forms a heterocyclic ring containing 3-7 carbon atoms and one or more heteroatoms;

B is selected from:

- (i) a direct bond;
 5 (ii) a group of Formula (IV)



Formula (IV)

wherein:

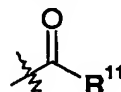
X is selected from N or CH,

- 10 wherein at position (a) Formula (IV) is attached to the nitrogen atom and the $(CH_2)_p$ group is attached to R^8 ; and

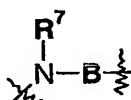
(iii) a group independently selected from: optionally substituted C_{1-6} alkylene, optionally substituted C_{3-7} cycloalkyl, optionally substituted C_{3-6} alkenylene, optionally substituted C_{3-6} alkynyl, C_{1-6} alkoxy, $(C_{1-5}alkyl)_{aa}-S(O_n)-(C_{1-5}alkyl)_{bb}$,

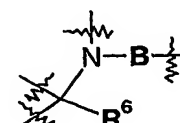
- 15 $(C_{1-5}alkyl)_{aa}-O-(C_{1-5}alkyl)_{bb}$ or $(C_{1-5}alkyl)_{aa}-N(R^{15})-(C_{1-5}alkyl)_{bb}$, wherein R^{15} and the $(C_{1-5}alkyl)_{aa}$ or $(C_{1-5}alkyl)_{bb}$ chain can be joined to form a ring;

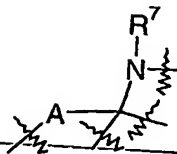
or the group $-B-R^8$ represents a group of Formula (V)



Formula (V);

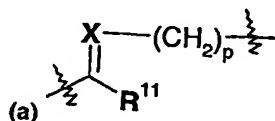
- 20 or the group  together forms a heterocyclic ring containing 5-7 carbons atoms;

or the group  forms a heterocyclic ring containing 3-7 carbon atoms and one or more heteroatoms;



or when R^3 is a group of Formula (IIa), (IIb), (IIc) or (IIId), the group forms a heterocyclic ring containing 3-7 carbon atoms and one or more heteroatoms; **B** is selected from:

- (i) a direct bond;
 5 (ii) a group of Formula (IV)



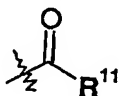
Formula (IV)

wherein:

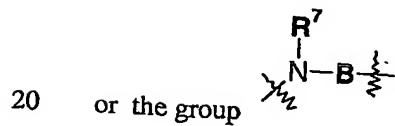
X is selected from N or CH,

- 10 wherein at position (a) Formula (IV) is attached to the nitrogen atom and the $(CH_2)_p$ group is attached to R^8 ; and

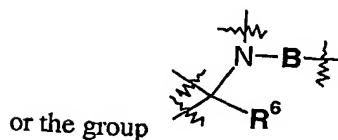
- (iii) a group independently selected from: optionally substituted C_{1-6} alkylene, optionally substituted C_{3-7} cycloalkyl, optionally substituted C_{3-6} alkenylene, optionally substituted C_{3-6} alkynyl, C_{1-6} alkoxy, $(C_{1-5}alkyl)_{aa}-S(O_n)-(C_{1-5}alkyl)_{bb}$,
 15 $(C_{1-5}alkyl)_{aa}-O-(C_{1-5}alkyl)_{bb}$ or $(C_{1-5}alkyl)_{aa}-N(R^{15})-(C_{1-5}alkyl)_{bb}$,
 wherein R^{15} and the $(C_{1-5}alkyl)_{aa}$ or $(C_{1-5}alkyl)_{bb}$ chain can be joined to form a ring;
 or the group $-B-R^8$ represents a group of Formula (V)



Formula (V);



together forms a heterocyclic ring containing 5-7 carbons atoms;



forms a heterocyclic ring containing 3-7 carbon atoms and one or more heteroatoms;

E is $-O-$, $-S(O_n)$, $-C(O)-$, $-NR^{15}$ or $-C(R^9R^{10})_q$;

F is $-E(CH_2)_r-$;

G is selected from: hydrogen, halo, N, O, $S(O_n)$, $C(O)$, $C(R^9R^{10})_t$, optionally substituted C_{2-6} alkenylene, optionally substituted C_{2-6} alkynylene or a direct bond to R^{18} ,

5 J is a group of the formula: $-(CH_2)_s-L-(CH_2)_s-$ wherein when s is greater than 0, the alkylene group is optionally substituted

K is selected from: a direct bond, $-O-(CH_2)_s-$, $-C(O)-(CH_2)_s-$, $-S(O_n)-(CH_2)_s-$, $-N(R^{18})-(CH_2)_s-$, $-OC(O)-(CH_2)_s-$, $-C(O)O-(CH_2)_s-$, $-OS(O_n)-(CH_2)_s-$, or $-S(O_n)-O-(CH_2)_s-$;

10 L is selected from optionally substituted aryl or optionally substituted heterocyclyl;
M is $-(CH_2)_{0-2}-O-$;

n is an integer between 0 and 2;

p is an integer between 0 and 4;

q is an integer between 0 and 4;

15 r is an integer between 0 and 4;

s is an integer between 0 and 4; and

t is an integer between 0 and 4;

with the proviso that

(i) when G is hydrogen or halo, then R^{17} and R^{18} are both absent;

20 (ii) when G is O, $S(O_n)$, $C(O)$ or $C(R^{11}R^{12})_t$, then G is substituted by a single group independently selected from the definition of R^{17} or R^{18} and when G is a direct bond to R^{18} then G is substituted by a single group selected from R^{18} ; and
or a salt, solvate or pro-drug thereof.

According to a further feature of the first aspect of the invention there is provided a
25 pharmaceutical formulation comprising a compound of Formula (I), or salt, pro-drug or solvate thereof, and a pharmaceutically acceptable diluent or carrier.

According to a further feature of the first aspect of the invention there is provided the following uses of a compound of Formula (I), or salt, pro-drug or solvate thereof:

- 30 (a) the use in the manufacture of a medicament for antagonising gonadotropin releasing hormone activity;
- (b) the use in the manufacture of a medicament for administration to a patient, for reducing the secretion of luteinizing hormone by the pituitary gland of the patient; and

- (c) the use in the manufacture of a medicament for administration to a patient, for therapeutically treating and/or preventing a sex hormone related condition in the patient.

According to a further aspect of the invention there is provided a method of

- ~~antagonising gonadotropin-releasing hormone-activity in a patient, comprising administering a~~
 5 compound of Formula (I), or salt, pro-drug or solvate thereof, to a patient.

Whilst pharmaceutically-acceptable salts of compounds of the invention are preferred, other non-pharmaceutically-acceptable salts of compounds of the invention may also be useful, for example in the preparation of pharmaceutically-acceptable salts of compounds of the invention.

- 10 In the present specification, unless otherwise indicated, an alkyl, alkylene, alkenyl or alkynyl moiety may be linear or branched. The term "alkylene" refers to the group $-\text{CH}_2-$. Thus, C_8 alkylene for example is $-(\text{CH}_2)_8-$. For avoidance of doubt the term C_0 alkyl within the group C_{0-5} alkyl is a direct bond.


The term "aryl" refers to phenyl or naphthyl.

- 15 The term "carbamoyl" refers to the group $-\text{C}(\text{O})\text{NH}_2$.

The term "halo" refers to fluoro, chloro, bromo or iodo.

- The term "heterocyclyl" or "heterocyclic ring" refers to a 5-10 membered aromatic mono or bicyclic ring or a 5-10 membered saturated or partially saturated mono or bicyclic ring, said aromatic, saturated or partially unsaturated rings containing up to 5 heteroatoms
 20 independently selected from nitrogen, oxygen or sulphur, linked via ring carbon atoms or ring nitrogen atoms where a bond from a nitrogen is allowed, for example no bond is possible to the nitrogen of a pyridine ring, but a bond is possible through the 1-nitrogen of a pyrazole ring. Examples of 5- or 6-membered aromatic heterocyclic rings include pyrrolyl, furanyl, imidazolyl, triazolyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyridinyl, isoxazolyl, oxazolyl,
 25 1,2,4 oxadiazolyl, isothiazolyl, thiazolyl and thienyl. A 9 or 10 membered bicyclic aromatic heterocyclic ring is an aromatic bicyclic ring system comprising a 6-membered ring fused to either a 5 membered ring or another 6 membered ring. Examples of 5/6 and 6/6 bicyclic ring systems include benzofuranlyl, benzimidazolyl, benzthiophenyl, benzthiazolyl, benzisothiazolyl, benzoxazolyl, benzisoxazolyl, indolyl, pyridoimidazolyl,
 30 pyrimidoimidazolyl, quinolinyl, isoquinolinyl, quinoxalinyl, quinazolinyl, phthalazinyl, cinnolinyl and naphthyridinyl. Examples of saturated or partially saturated heterocyclic rings include pyrrolinyl, pyrrolidinyl, morpholinyl, piperidinyl, piperazinyl, dihydropyridinyl and dihydropyrimidinyl.

The term "aromatic ring" refers to a 5-10 membered aromatic mono or bicyclic ring optionally containing up to 5 heteroatoms independently selected from nitrogen, oxygen or sulphur. Examples of such "aromatic rings" include: phenyl, pyrrolyl, furanyl, imidazolyl, triazolyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyridinyl, isoxazolyl, oxazolyl, 1,2,4-oxadiazolyl, isothiazolyl, thiazolyl and thienyl. Preferred aromatic rings include phenyl, thienyl and pyridyl.

The symbol  denotes where the respective group is linked to the remainder of the molecule.

The term **C₁₋₃perfluoroalkyl** refers to a C₁₋₃alkyl chain in which all hydrogens have been replaced with a fluorine atom. Examples of **C₁₋₃perfluoroalkyl** include trifluoromethyl, pentafluoroethyl and 1-trifluoromethyl-1,2,2,2-tetrafluoroethyl-. Preferably **C₁₋₃perfluoroalkyl** is trifluoromethyl.

Examples of **C₁₋₈alkyl** include: methyl, ethyl, propyl, isopropyl, butyl, *iso*-butyl, *tert*-butyl and 2-methyl-pentyl; example of **C₁₋₈alkylene** include: methylene, ethylene and 2-methyl-propylene; examples of **C₁₋₆alkenyl** include allyl (2-propenyl) and 2-butenyl, examples of **C₁₋₆alkynyl** 2-propynyl and 3-butylnyl, examples of **haloC₁₋₆alkyl** include fluoroethyl, chloropropyl and bromobutyl, examples of **hydroxyC₁₋₆alkyl** include hydroxymethyl, hydroxyethyl and hydroxybutyl, examples of **C₁₋₈alkoxy** include methoxy, ethoxy and butyloxy; examples of **C₁₋₄alkoxyC₁₋₄alkyl** include methoxyethyl, propoxybutyl and propoxymethyl, examples of **C₁₋₆alkanoyl** include formyl, ethanoyl, propanoyl or pentanoyl, examples of **N-C₁₋₄alkylamino** include N-methylamino and N-ethylamino; examples of **N,N-di-C₁₋₄alkylamino** include N,N-dimethylaminoethyl, N,N-di-methylaminopropyl and N,N-dipropylaminoethyl, examples of **HO-C₂₋₄alkyl-NH** include hydroxymethylamino hydroxyethylamino and hydroxypropylamino, examples of **HO-C₂₋₄alkyl-N(C₁₋₄alkyl)** include N-methyl-hydroxymethylamino, N-ethyl-hydroxyethylamino, and N-propyl-hydroxypropylamino, examples of **C₁₋₆alkyl-S(O_n)-methylthio, methylsulphanyl, ethylsulphanyl, ethylsulphonyl and propylsulphonyl, include examples of **arylC₁₋₆alkyl** include benzyl, phenethyl and phenylbutyl, examples of **heterocyclylC₁₋₆alkyl** include pyrrolidin-1-yl ethyl, imidazolylethyl, pyridylmethyl and pyrimidinylethyl.**

It is to be understood that, insofar as certain of the compounds of the invention may exist in optically active or racemic forms by virtue of one or more asymmetric carbon atoms,

the invention includes in its definition any such optically active or racemic form which possesses the property of antagonizing gonadotropin releasing hormone (GnRH) activity. The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic form. Similarly, activity of these compounds may be evaluated using the standard laboratory techniques referred to hereinafter.

The invention also relates to any and all tautomeric forms of the compounds of the different features of the invention that possess the property of antagonizing gonadotropin releasing hormone (GnRH) activity.

It will also be understood that certain compounds of the present invention may exist in solvated, for example hydrated, as well as unsolvated forms. It is to be understood that the present invention encompasses all such solvated forms which possess the property of antagonizing gonadotropin releasing hormone (GnRH) activity.

Preferred compounds of Formula (I), Formula (Ia) and Formula (Ib) are those wherein any one of the following apply.

Preferably R^1 is selected from hydrogen or optionally substituted C_{1-6} alkyl. More preferably R^1 represents hydrogen, methyl, ethyl or *tert*-butyl. Most preferably R^1 represents hydrogen.

Preferably optional substituents on R^1 are independently selected from: optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, cyano, nitro, C_{1-3} perfluoroalkyl, C_{1-3} perfluoroalkoxy, optionally substituted aryl, optionally substituted aryl C_{1-6} alkyl, $R^9O(CH_2)_v$ -, $R^9C(O)O(CH_2)_v$ -, $R^9OC(O)(CH_2)_v$ -, $R^{16}S(O_n)(CH_2)_v$ -, $R^9R^{10}NC(O)(CH_2)_v$ -, or halo wherein v is an integer between 0 and 4, and where 2 optional substituents are present together they can optionally form a C_{3-7} carbocyclic ring or a heterocyclic ring.

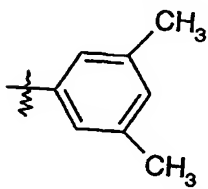
Preferably R^2 is an optionally substituted monocyclic aromatic ring structure. Most preferably R^2 represents optionally substituted phenyl.

Preferably optional substituents on R^2 are independently selected from: optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, cyano, nitro, C_{1-3} perfluoroalkyl, C_{1-3} perfluoroalkoxy, optionally substituted aryl, optionally substituted aryl C_{1-6} alkyl, $R^9O(CH_2)_w$ -, $R^9C(O)O(CH_2)_w$ -, $R^9OC(O)(CH_2)_w$ -, $R^{16}S(O_n)(CH_2)_w$ -, $R^9R^{10}NC(O)(CH_2)_w$ -, $R^9R^{10}N$ - or halo; wherein w is an integer between 0 and 4 and R^9 and R^{10} are as defined above. Further preferably the optional substituents on R^2 are independently selected from cyano, R^6R^fN -, optionally substituted C_{1-6} alkyl (preferably, C_{1-4} alkyl, eg, methyl or ethyl),

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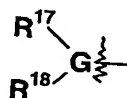
optionally substituted C_{1-6} alkoxy (preferably, C_{1-4} alkoxy, eg, methoxy, ethoxy or *tert*-butoxy) or halo (eg, F, Br or Cl) wherein R^e and R^f are independently selected from hydrogen, C_{1-6} alkyl or aryl. Yet further preferably optional substituents on R^2 are independently selected from methyl, ethyl, methoxy, ethoxy, *tert*-butoxy, F or Cl. Most preferably optional substituents on R^2 are independently selected from methyl, F or Cl. Preferably R^2 bears 1, 2 or 3 substituents.

Most preferably R^2 represents



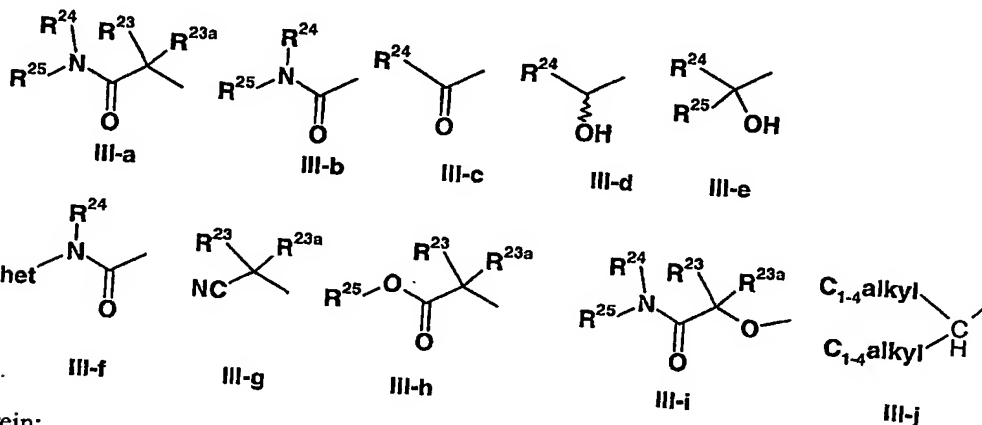
Preferably R^3 is selected from a group of Formula (IIa) or Formula (IIb). Most preferably R^3 is a group of Formula (IIb).

Preferably the group of Formula (III):



Formula (III)

is selected from a group of Formula III-a; III-b; III-c; III-d; III-e; III-f, III-g, III-h, III-i or III-j;



wherein:


het represents an optionally substituted 3- to 8- membered heterocyclic ring containing from 1 to 4 heteroatoms independently selected from O, N and S;

R^{23} and R^{23a} are independently selected from:

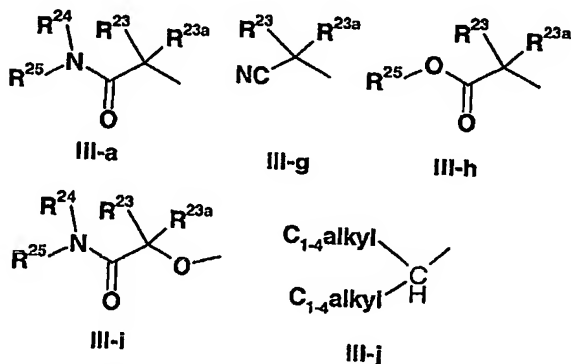
- 12 -

- (i) hydrogen or optionally substituted C_{1-8} alkyl; or
 (ii) R^{23} and R^{23a} together with the carbon to which they are attached form an optionally substituted 3 to 7-membered cycloalkyl ring;

R^{24} and R^{25} are selected from:

- 5 (i) R^{24} selected from hydrogen; optionally substituted C_{1-8} alkyl; optionally substituted aryl; $-R^d-Ar$, where R^d represents C_{1-8} alkylene and Ar represents optionally substituted aryl; and optionally substituted 3- to 8- membered heterocyclic ring optionally containing from 1 to 3 further heteroatoms independently selected from O, N and S; and R^{25} is selected from hydrogen; optionally substituted C_{1-8} alkyl and optionally substituted aryl;
- 10 (ii) wherein the group of Formula (III) represents a group of Formula III-a, III-b or III-i, then the group $NR^{24}(-R^{25})$ represents an optionally substituted 3- to 8-membered heterocyclic ring optionally containing from 1 to 3 further heteroatoms independently selected from O, N and S; or
- 15 (iii) wherein the group of Formula (III) represents structure III-e,  represents an optionally substituted 3- to 8- membered heterocyclic ring optionally containing from 1 to 4 heteroatoms independently selected from O, N and S;

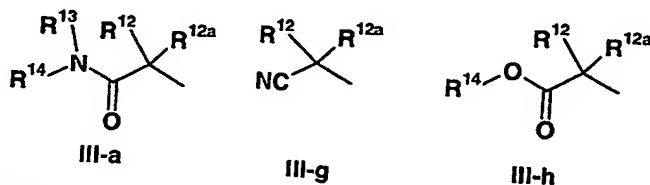
More preferably the group of Formula (III) is selected from a group of Formula III-a, III-g, III-h, or III-i:



wherein R^{23} , R^{23a} , R^{24} and R^{25} are as defined above.

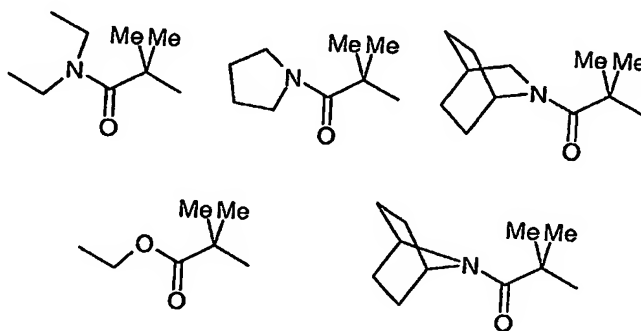
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Further preferably the group of Formula (III) is selected from one of the following groups:



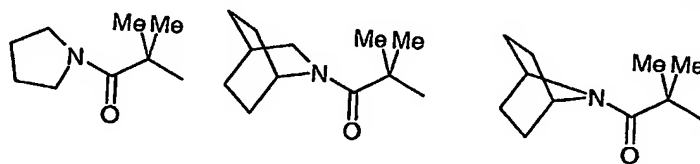
wherein R^{23} , R^{23a} , R^{24} and R^{25} are as defined above.

5 Yet further preferably the group of Formula (III) is selected from one of the following groups:



wherein Me represents methyl.

Most preferably the group of Formula (III) is selected from one of the following groups:



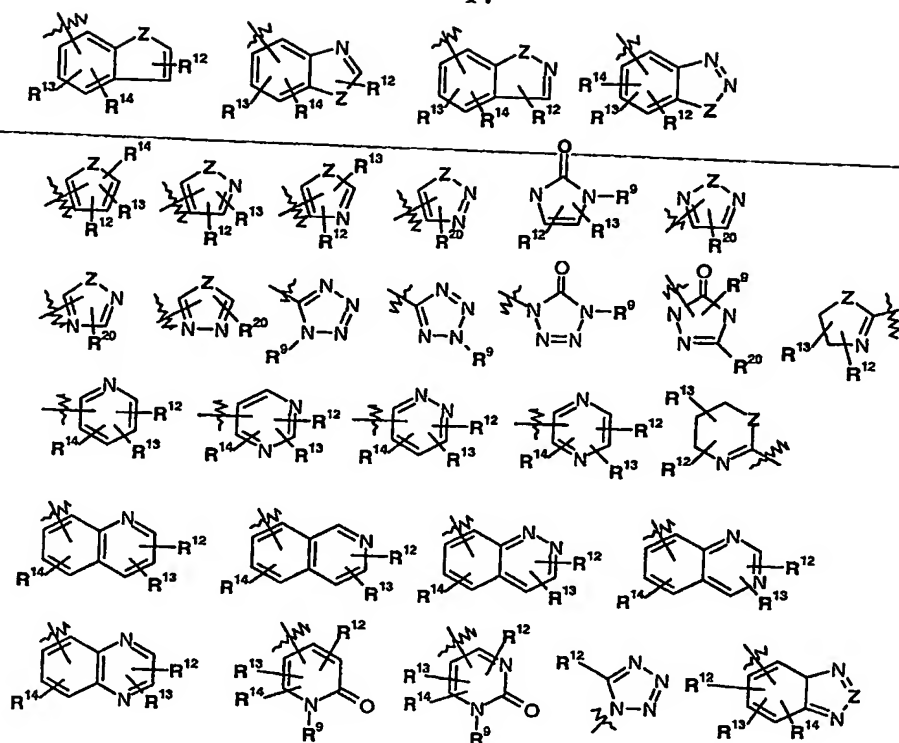
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Preferably R^6 and R^{6a} are independently selected from hydrogen or optionally substituted C_{1-6} alkyl, more preferably independently selected from hydrogen and unsubstituted C_{1-6} alkyl, more preferably independently selected from hydrogen or methyl.

Preferably R^7 is selected from: hydrogen or C_{1-4} alkyl. More preferably R^7 is hydrogen or methyl. Most preferably R^7 is hydrogen.

15 When R^8 is heterocyclyl then R^8 is preferably selected from one of the following groups:

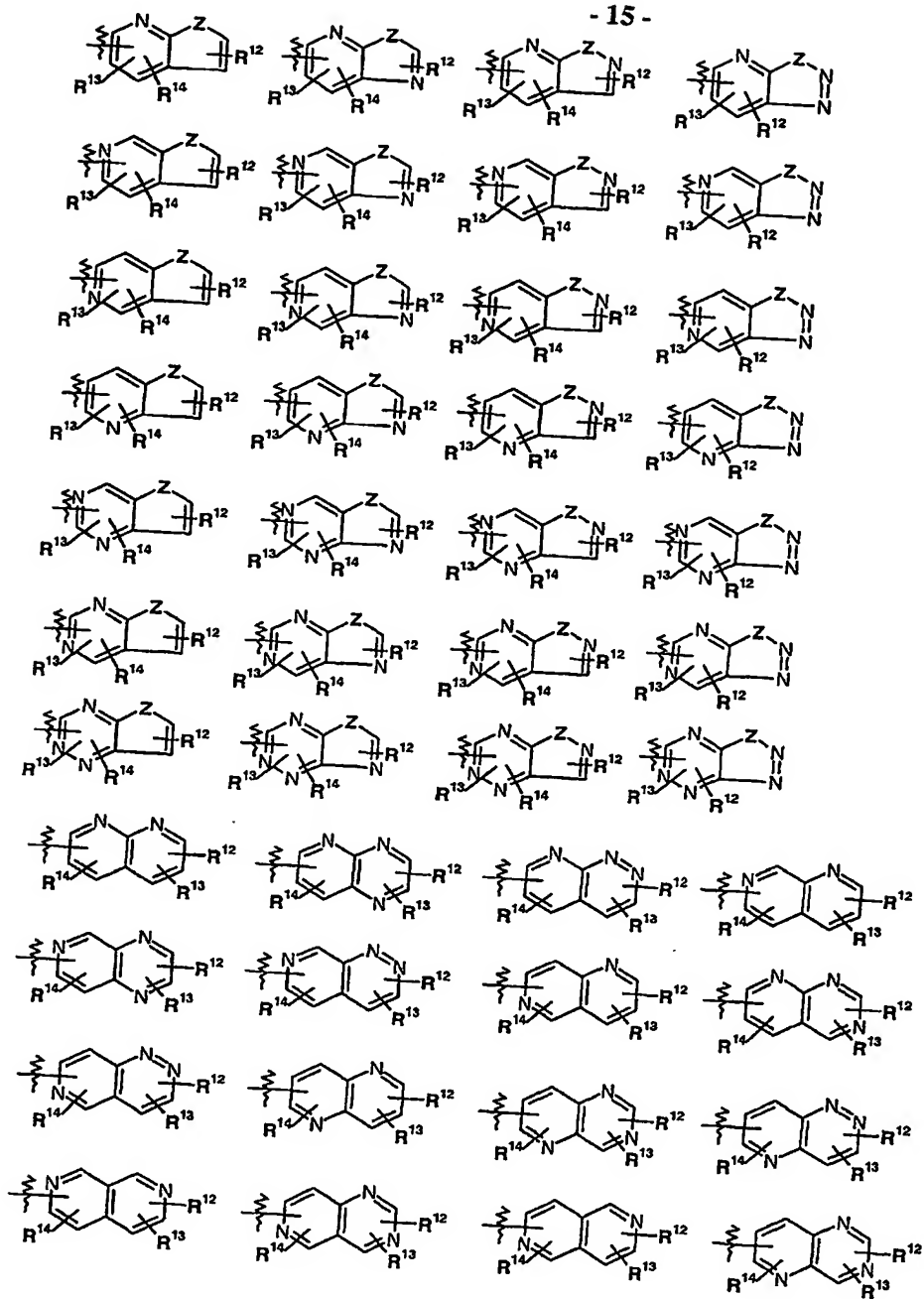
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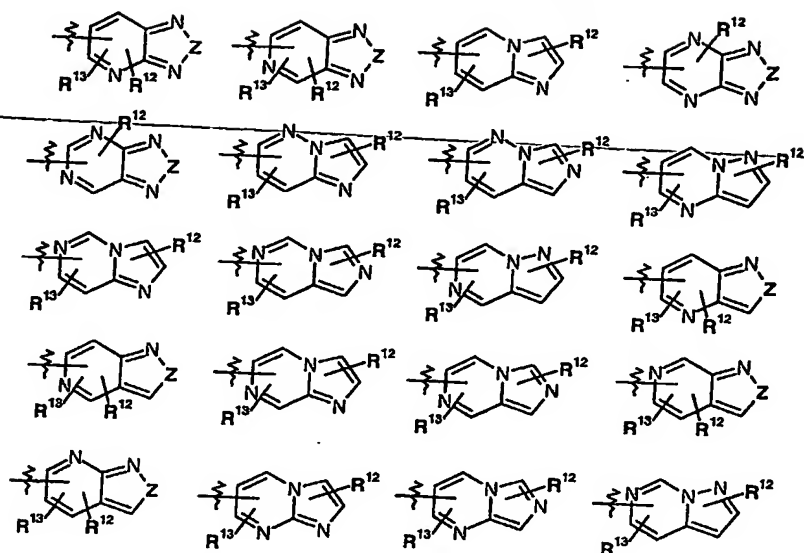


wherein Z is selected from: O, S or N(R⁹), R²⁰ is selected from any group within the definitions of R¹² and R¹³, and R⁹, R¹², R¹³ and R¹⁴ are as defined above.

In a further embodiment of the invention when R⁸ is heterocyclyl then R⁸ is preferably
5 selected from one of the following groups:

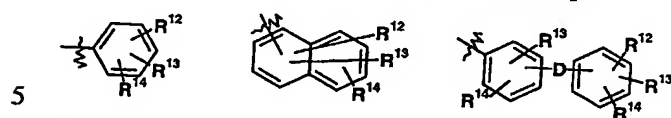
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wherein Z is selected from: O, S or N(R⁹) and R⁹, R¹² and R¹³ are as defined above.

When R⁸ is aryl or aryl-(C)-aryl optionally substituted by R¹², R¹³ and R¹⁴, R⁸ is preferably selected one of the following groups:



wherein D is selected from group E, group F or a direct bond;

Preferably R⁸ is selected from hydrogen, cyano, C₁₋₄alkyl (more preferably methyl), C₂₋₆alkynyl (more preferably 2-propynyl), hydroxyC₁₋₆alkyl (more preferably hydroxyethyl), C₁₋₄alkoxyC₁₋₄alkyl (more preferably methoxyethyl), haloC₁₋₆alkyl (more preferably fluoroethyl), C₁₋₄alkanoyl (more preferably formyl), C₁₋₄alkoxycarbonyl (more preferably butyloxycarbonyl), N,N-di-C₁₋₄alkylamino (more preferably N,N-dimethylaminoethyl and N,N-dimethylaminopropyl), C₁₋₆alkyl-S(O)_n- (more preferably ethylsulphonyl), cyclopentyl, phenyl, benzyl, cyanophenyl, pyrrolidinyl, pyrrolidylethyl, imidazolyl, imidazolylC₁₋₆alkyl (more preferably imidazolylethyl), thiazolyl, pyridyl, pyridylC₁₋₆alkyl (more preferably pyridylmethyl) or pyrimidyl wherein a phenyl or heterocyclyl ring is optionally substituted by C₁₋₄alkyl or halo.

When R⁹ and/or R¹⁰ is a component of group G, R⁹ and R¹⁰ are preferably independently selected from hydrogen, optionally substituted C₁₋₆alkyl, optionally substituted aryl, optionally substituted arylC₁₋₆alkyl or R⁹ and R¹⁰ forms C₃₋₇cycloalkyl or heterocyclyl.

Further preferably hydrogen or C_{1-4} alkyl. Most preferably hydrogen or methyl. Most preferably both R^9 and R^{10} are methyl.

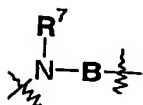
When R^9 and/or R^{10} is a component of group R^{18} , R^9 and R^{10} are preferably independently selected from hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted aryl, optionally substituted aryl C_{1-6} alkyl or R^9 and R^{10} forms C_{3-7} cycloalkyl or heterocyclyl. Further preferably when R^9 is a component of group R^{18} , R^9 is preferably heterocyclyl. Most preferably pyrrolidinyl, 7-azabicyclo[2.2.1]hept-7-yl or 3-azabicyclo[3.2.2]nonyl.

Preferably R^{17} is hydrogen, hydroxy, cyano or is absent. Most preferably R^{17} is absent.

Preferably R^{18} is selected from hydrogen, $R^9N(R^{10})C(O)-$, $R^9C(O)-$, $R^9OC(O)-$ or $R^{18a}-C(R^9R^{10})-$ wherein R^{18a} is $R^9N(R^{10})C(O)-$. Further preferably $R^9C(O)-$. Most preferably $R^9C(O)-$ wherein R^9 is heterocyclyl..

Preferably A is selected from optionally substituted C_{1-5} alkylene. Further preferably A is selected from C_{1-5} alkylene optionally substituted with C_{1-4} alkyl. Yet further preferably A is unsubstituted C_{1-2} alkylene. Most preferably methylene.

15 Preferably B is selected from optionally substituted C_{1-6} alkylene or the group



forms a C_{5-7} heterocyclic ring. Preferably unsubstituted C_{6-6} alkylene or a C_{5-7} heterocyclic saturated ring. Most preferably methylene, ethylene, propylene, butylene or piperazinyl.

Preferably G is a direct bond, $-O-$ or $-C(R^9R^{10})-$. More preferably $-C(R^9R^{10})-$. Most preferably $-C(CH_3)_2-$.

Preferably M is $-CH_2-O-$.

Preferably optional substituents on heterocyclyl groups in R^8 , R^9 , R^{10} , R^{18} and R^{19} or on heterocyclyl groups formed when R^{17} and R^{18} together form a heterocyclic ring are selected from: optionally substituted C_{1-6} alkyl, C_{1-6} alkoxy, optionally substituted C_{2-6} alkenyl, cyano, 25 nitro, C_{1-3} perfluoroalkyl, C_{1-3} perfluoroalkoxy, optionally substituted aryl, optionally substituted aryl C_{1-6} alkyl, $R^9O(CH_2)_p-$, $R^9C(O)O(CH_2)_w-$, $R^9OC(O)(CH_2)_w-$, $R^{16}S(O)_n(CH_2)_w-$, $R^9R^{10}NC(O)(CH_2)_w-$ or halo; wherein w is an integer between 0 and 4 and p, R^9 , R^{10} and R^{16} are as defined above.

Preferably the optional substituents on alkyl, alkenyl, alkynyl, cycloalkyl and aryl 30 groups are independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-7} cycloalkyl, optionally substituted aryl, optionally substituted aryl C_{1-6} alkyl, hydroxy, oxo, cyano, C_{1-6} alkoxy, halo

(preferably fluoro), $R^{16}S(O_n)(CH_2)_w-$, $R^9OC(O)-$, optionally substituted aryl C_{1-3} alkoxy wherein R^9 is as defined above.

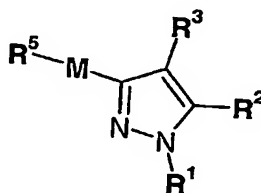
Preferably the optional substituents on optionally substituted aryl and aryl C_{1-6} alkyl groups are selected from: optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, 5 cyano, nitro, halo (preferably fluoro), C_{1-3} perfluoroalkyl, C_{1-3} perfluoroalkoxy, optionally substituted aryl, optionally substituted aryl C_{1-6} alkyl, $R^9O(CH_2)_p-$, $R^9C(O)O(CH_2)_w-$, $R^9OC(O)(CH_2)_w-$, $R^{16}S(O_n)(CH_2)_w-$, $R^9R^{10}NC(O)(CH_2)_w-$ or halo; wherein w is an integer between 0 and 4 and n , R^9 and R^{10} are as defined above..

In preferences for heterocyclyl in R^8 the nitrogen atoms contained in R^8 heteroaromatic 10 rings exist either as drawn or, where chemically allowed, in their oxidised ($N \rightarrow O$, $N-OH$) state.

Where optional substitution is mentioned at various places the optional substituents also comprise the following definition which refers to one, two, three or more optional substituents. Unless otherwise indicated above (i.e., where a list of optional substituents is 15 specifically listed within a definition), each substituent can be independently selected from C_{1-8} alkyl (eg, C_{2-6} alkyl, and most preferably methyl, ethyl or *tert*-butyl); C_{3-8} cycloalkoxy, preferably cyclopropoxy, cyclobutoxy or cyclopentoxo; C_{1-6} alkoxy, preferably methoxy or C_{2-4} alkoxy; halo, preferably Cl or F; Hal_3C- , Hal_2CH- , $HalCH_2-$, Hal_3CO- , Hal_2CHO or $HalCH_2O$, wherein Hal represents halo (preferably F); R^gCH_2O- , $R^hC(O)N(R)-$, $R^hSO_2N(R)-$ or 20 R^g-R^hN- , wherein R^g and R^h independently represent hydrogen or C_{1-8} alkyl (preferably methyl or C_{2-6} alkyl or C_{2-4} alkyl), or R^g-R^hN- represents an optionally substituted C_{3-8} , preferably C_{3-6} , heterocyclic ring optionally containing from 1 to 3 further heteroatoms independently selected from O, N and S; hydrogen; or $R^kC(O)O-$ or $R^kC(O)-$, R^k representing hydrogen, optionally substituted phenyl or C_{1-6} alkyl (preferably methyl, ethyl, *iso*-propyl or 25 *tert*-butyl). For optional substitution of the heterocyclic ring represented by R^g-R^hN- , at least one (eg, one, two or three) substituents may be provided independently selected from C_{1-6} alkyl (eg, C_{2-4} alkyl, more preferably methyl); phenyl; CF_3O- ; F_2CHO- ; C_{1-8} alkoxy, preferably methoxy, ethoxy or C_{3-6} alkoxy; C_{1-8} alkoxy $C(O)$, preferably methoxycarbonyl, ethoxycarbonyl, *tert*-butoxycarbonyl or C_{3-6} alkoxy $C(O)-$; phenoxycarbonyl; phenoxy; 30 C_{1-8} alkanoyl, preferably acetyl, ethanoyl or C_{3-6} alkylanoyl; carboxy; C_{1-8} alkyl $S(O_{nn})$ wherein nn is an integer between 0 and 2, preferably methylthio, ethylthio, C_{3-6} alkylthio, methylsulphinyl, ethylsulphinyl, C_{3-6} alkylsulphinyl, methylsulphonyl, ethylsulphonyl or C_{3-6} alkylsulphonyl; hydroxy; halo (eg, F, Cl or Br); R^mR^nN- where R^m and R^n are

independently hydrogen or C₁₋₆alkyl (preferably C₂₋₄alkyl, more preferably methyl, most preferably R^m=Rⁿ=methyl); and nitro.

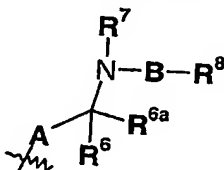
According to a further aspect of the invention there is provided a compound of Formula (Ia)



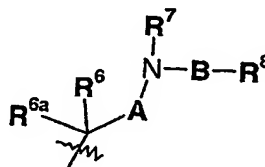
Formula (Ia)

wherein

R³ is selected from a group of Formula (IIa) or Formula (IIb):



Formula (IIa)



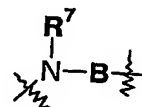
Formula (IIb)

and R¹, R², R⁵, R⁶, R^{6a}, R⁷, R⁸, A, B and M are as defined above; or salt, solvate or pro-drug thereof.

A further preferred group of compounds of the invention comprises a compound of Formula (Ia), wherein:

A is optionally substituted C₁₋₅alkylene;

B is selected from optionally substituted C₁₋₆alkylene or the group



forms a

M is -CH₂-O-;

R¹ is hydrogen or C₁₋₄alkyl;

R⁶ and R^{6a}, are independently selected from hydrogen and optionally substituted C₁₋₆alkyl;

R⁷ is selected from: hydrogen or C₁₋₄alkyl;

R⁸ is selected from hydrogen, cyano, C₁₋₆alkyl, haloC₁₋₆alkyl, C₂₋₆alkynyl, C₁₋₆alkanoyl, C₁₋₄alkoxyC₁₋₄alkyl, C₁₋₆alkoxycarbonyl, N,N-di-C₁₋₄alkylamino, aryl, arylC₁₋₆alkyl, C₃₋₇cycloalkyl, C₃₋₇cycloalkylC₁₋₆alkyl, heterocyclyl, heterocyclylC₁₋₆alkyl, or

heterocyclylcarbonylC₁₋₄alkyl wherein aryl and heterocyclyl rings are optionally substituted by cyano and C₁₋₄alkyl; and

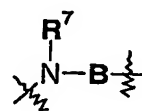
R² and R⁵; are as defined above

or salt, solvate or pro-drug thereof.

- 5 A further preferred group of compounds of the invention comprises a compound of Formula (Ia), wherein:

A is optionally substituted C₁₋₅alkylene;

B is selected from optionally substituted C₁₋₆alkylene or the group



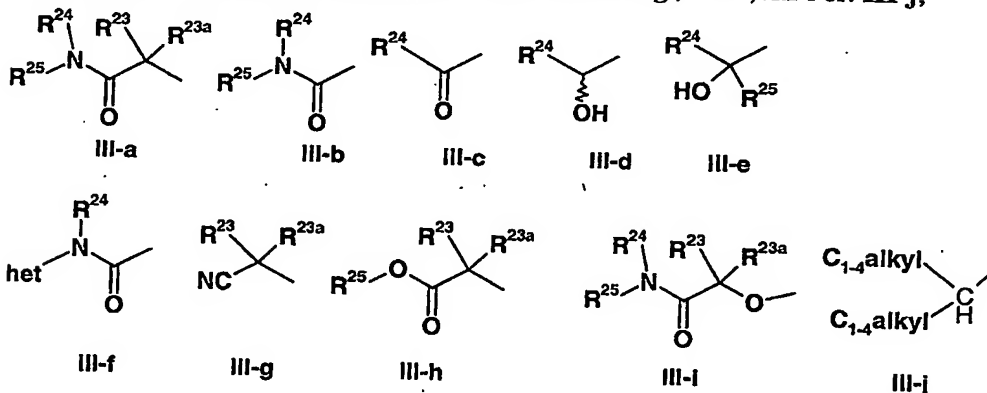
forms a

ring containing C₅₋₇heterocyclic ring;

- 10 R¹ is hydrogen or C₁₋₄alkyl, preferably hydrogen;

R² is an optionally substituted monocyclic aromatic ring structure, preferably optionally substituted phenyl, most preferably 3,5-dimethylphen-1-yl;

R⁵ is a group of Formula (III) wherein the group of Formula (III) is selected from a group of Formula III-a; III-b; III-c; III-d; III-e; III-f, III-g, III-h, III-i or III-j;



15

wherein R²³, R^{23a}, R²⁴ and R²⁵ are as defined above, preferably the group of Formula (III) is selected from (III-a), (III-g) and (III-h);

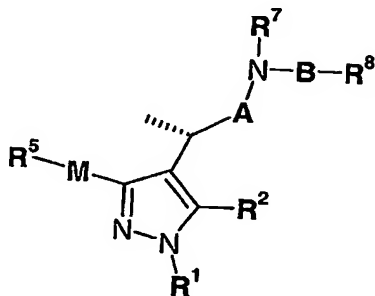
R⁶ and R^{6a}, are independently selected from hydrogen and optionally substituted C₁₋₆alkyl;

R⁷ is selected from: hydrogen or C₁₋₄alkyl;

- 20 R⁸ is selected from hydrogen, cyano, C₁₋₆alkyl, haloC₁₋₆alkyl, C₂₋₆alkynyl, C₁₋₆alkanoyl, C₁₋₄alkoxyC₁₋₄alkyl, C₁₋₆alkoxycarbonyl, N,N-di-C₁₋₄alkylamino, aryl, arylC₁₋₆alkyl, C₃₋₇cycloalkyl, C₃₋₇cycloalkylC₁₋₆alkyl, heterocyclyl, heterocyclylC₁₋₆alkyl, or heterocyclylcarbonylC₁₋₄alkyl wherein aryl and heterocyclyl rings are optionally substituted by cyano and C₁₋₄alkyl; and

R^2 , and R^5 ; are as defined above
or salt, solvate or pro-drug thereof.

A further preferred group of compounds of the invention comprises a compound of Formula (Ib):



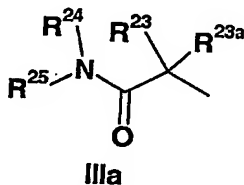
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Formula (Ib)

Wherein R^1 , R^2 , R^5 ; R^7 , R^8 , A , B and M are as defined above
or salt, solvate or pro-drug thereof.

A yet further preferred group of compounds of the invention comprises a compound of
10 Formula (I), (Ia) or (Ib) wherein:

R^5 is a group of Formula (III) wherein the group of Formula (III) is a group of
formula IIIa:



IIIa

wherein R^{23} , R^{23a} , R^{24} and R^{25} are as defined above;

15 or a salt, pro-drug or solvate thereof.

According to a further aspect of the invention there is provided a compound of Formula (I), or salt, solvate or pro-drug thereof, wherein R^3 is selected from a group of Formula (IIc) or Formula (IId) and R^1 , R^2 and R^5 are as defined above.

According to a further aspect of the invention there is provided a compound of Formula
20 (I), or salt, solvate or pro-drug thereof, wherein R^3 is selected from a group of Formula (IIe) or Formula (IIf) and R^1 , R^2 and R^5 are as defined above.

According to a further aspect of the invention there is provided a compound of Formula (I), or salt, solvate or pro-drug thereof, wherein R^3 is selected from a group of Formula (IIa), Formula (IIc) or Formula (IIe) and R^1 , R^2 and R^5 are as defined above.

According to a further aspect of the invention there is provided a compound of Formula (I), or salt, solvate or pro-drug thereof, wherein R^3 is selected from a group of Formula (IIb), Formula (IIc) or Formula (IIe) and R^1 , R^2 and R^5 are as defined above.

Particularly preferred compounds according to the present invention are wherein the

5 compound is selected from:

2-[3-(2,2-dimethyl-3-oxo-3-pyrrolidin-1-ylpropoxy)-5-(3,5-dimethylphenyl)-1H-pyrazol-4-yl]-N-(2-pyridin-4-ylethyl)ethanamine;

2-[3-(2,2-dimethyl-3-oxo-3-pyrrolidin-1-ylpropoxy)-5-(3,5-dimethylphenyl)-1H-pyrazol-4-yl]-N-(2-pyridin-4-ylbutyl)ethanamine;

10 2-[3-(2,2-dimethyl-3-oxo-3-(7-azabicyclo[2.2.1]hept-7-yl)propoxy)-5-(3,5-dimethylphenyl)-1H-pyrazol-4-yl]-N-(2-pyridin-4-ylethyl)ethanamine; and

2-[3-(2,2-dimethyl-3-oxo-3-(7-azabicyclo[2.2.1]hept-7-yl)propoxy)-5-(3,5-dimethylphenyl)-1H-pyrazol-4-yl]-N-(2-pyridin-4-ylbutyl)ethanamine;

or a salt, pro-drug or solvate thereof.

15 The compounds of Formula (I) may be administered in the form of a pro-drug which is broken down in the human or animal body to give a compound of the Formula (I). Examples of pro-drugs include in-vivo hydrolysable esters of a compound of the Formula (I).

Various forms of pro-drugs are known in the art. For examples of such pro-drug derivatives, see:

- 20 a) Design of Prodrugs, edited by H. Bundgaard, (Elsevier, 1985) and Methods in Enzymology, Vol. 42, p. 309-396, edited by K. Widder, et al. (Academic Press, 1985);
- b) A Textbook of Drug Design and Development, edited by Krogsgaard-Larsen and H. Bundgaard, Chapter 5 "Design and Application of Prodrugs", by H. Bundgaard p. 113-191 (1991);
- 25 c) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992);
- d) H. Bundgaard, et al., Journal of Pharmaceutical Sciences, 77, 285 (1988); and
- e) N. Kakeya, et al., Chem Pharm Bull, 32, 692 (1984).

An in-vivo hydrolysable ester of a compound of the Formula (I) containing a
30 carboxy or a hydroxy group is, for example, a pharmaceutically-acceptable ester which is hydrolysed in the human or animal body to produce the parent acid or alcohol. Suitable pharmaceutically-acceptable esters for carboxy include C_{1-6} alkoxymethyl esters for example methoxymethyl, C_{1-6} alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl

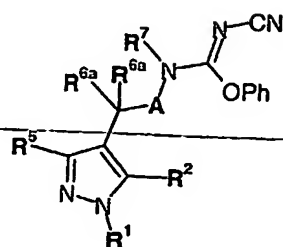
esters, C₃₋₈cycloalkoxycarbonyloxyC₁₋₆alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters, for example 5-methyl-1,3-dioxolen-2-onylmethyl; and C₁₋₆alkoxycarbonyloxyethyl esters.

An in-vivo hydrolysable ester of a compound of the Formula (I) containing a hydroxy group includes inorganic esters such as phosphate esters (including phosphoramidic cyclic esters) and α -acyloxyalkyl ethers and related compounds which as a result of the in-vivo hydrolysis of the ester breakdown to give the parent hydroxy group/s. Examples of α -acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxy-methoxy. A selection of in-vivo hydrolysable ester forming groups for hydroxy include alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, alkoxycarbonyl (to give alkyl carbonate esters), dialkylcarbamoyl and N-(dialkylaminoethyl)-N-alkylcarbamoyl (to give carbamates), dialkylaminoacetyl and carboxyacetyl.

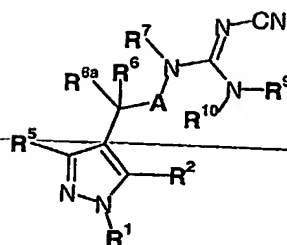
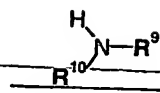
A suitable pharmaceutically-acceptable salt of a compound of the invention is, for example, an acid-addition salt of a compound of the invention which is sufficiently basic, for example, an acid-addition salt with, for example, an inorganic or organic acid, for example hydrochloric, hydrobromic, sulphuric, phosphoric, trifluoroacetic, citric or maleic acid. In addition a suitable pharmaceutically-acceptable salt of a compound of the invention which is sufficiently acidic is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium or magnesium salt, an ammonium salt or a salt with an organic base which affords a physiologically-acceptable cation, for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

The compounds of Formula (I) wherein R³ is a group of Formula (IIb) and B is a group of Formula (V) can be prepared by a process comprising a step selected from (a) to (f) as follows, these processes are provided as a further feature of the invention:-

- (a) for compounds wherein X is N and R⁸ is CN, reaction of a compound of formula XXXII as follows

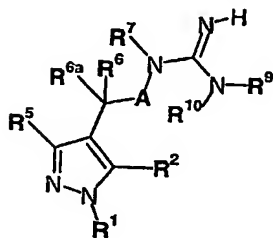


XXXII



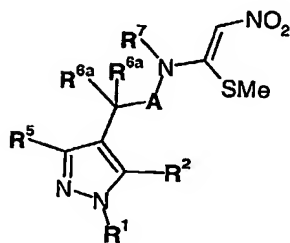
XXXIII

- (b) for compounds wherein X is N and R⁸ is hydrogen, cleavage of the cyano group of compound of formula XXXIII in the presence of acid to produce compound of formula XXXIV

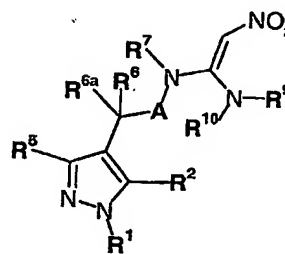
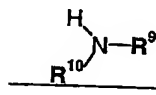


5 XXXIV

- (c) for compounds wherein X is CH and R⁸ is NO₂, reaction of compound of formula XXXV as follows

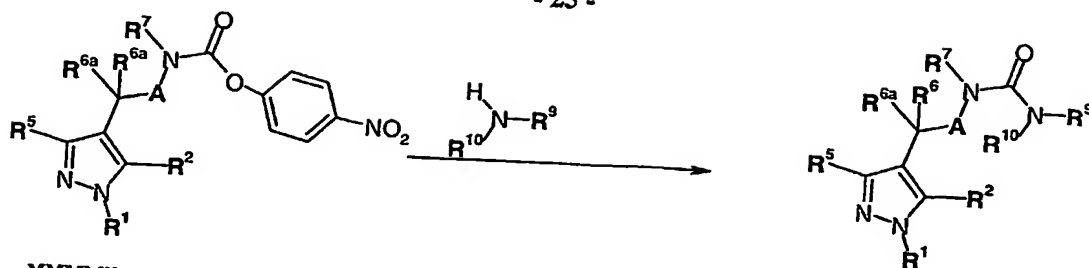


XXXV



XXXVI

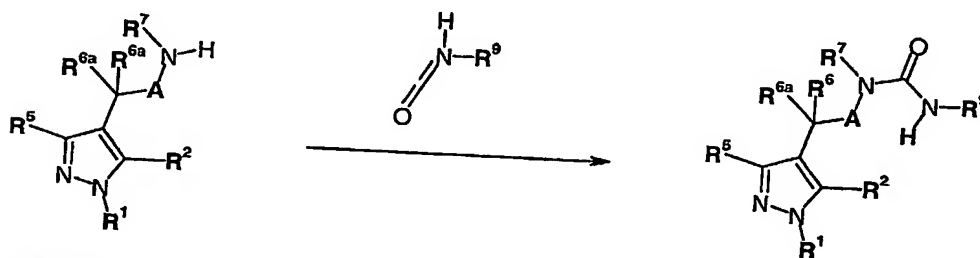
- (d) for compounds where X-R⁸ is O, reaction of compound of formula XXXVII as follows



XXXVII

XXXVIII

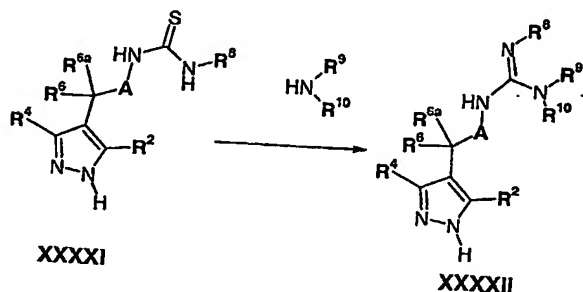
- (e) for compounds where $X-R^8$ is O, reaction of compound of formula XXXIX as follows



XXXIX

XXXX

- 5 (f) to form a compound wherein X is nitrogen and Reaction of a compound of formula XXXXI as follows



XXXXI

XXXXII

and thereafter if necessary:

- i) converting a compound of the Formula (I) into another compound of the Formula (I);
- 10 ii) removing any protecting groups;
- iii) forming a salt, pro-drug or solvate.

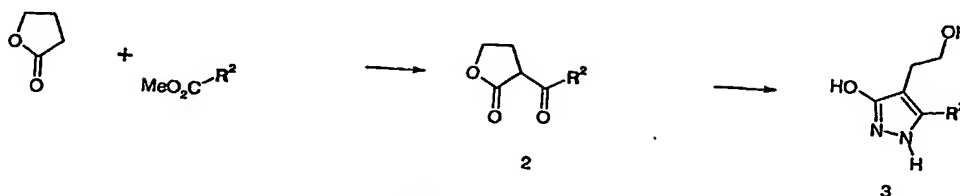
It will be appreciated by those skilled in the art that in the processes of the present invention certain functional groups such as hydroxyl or amino groups in the starting reagents or intermediate compounds may need to be protected by protecting groups. Thus, the preparation of the compounds of Formula (I) may involve, at an appropriate stage, the addition and subsequent removal of one or more protecting groups.

The protection and de-protection of functional groups is described in 'Protective Groups in Organic Chemistry', edited by J.W.F. McOmie, Plenum Press (1973) and 'Protective Groups in Organic Synthesis', 2nd edition, T.W. Greene and P.G.M. Wuts, Wiley-Interscience (1991).

- 5 A suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxy carbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or *tert*-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The de-protection conditions for the above protecting groups necessarily vary with the choice of
- 10 protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxy carbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a *tert*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid and an
- 15 arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.
- 20 - A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The de-protection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with
- 25 a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis

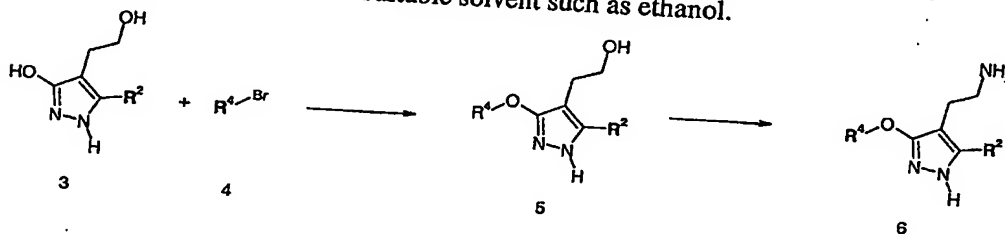
30 with a base such as sodium hydroxide, or for example a *tert*-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

EXPERIMENTAL**GENERAL REACTION SCHEMES**

Scheme a

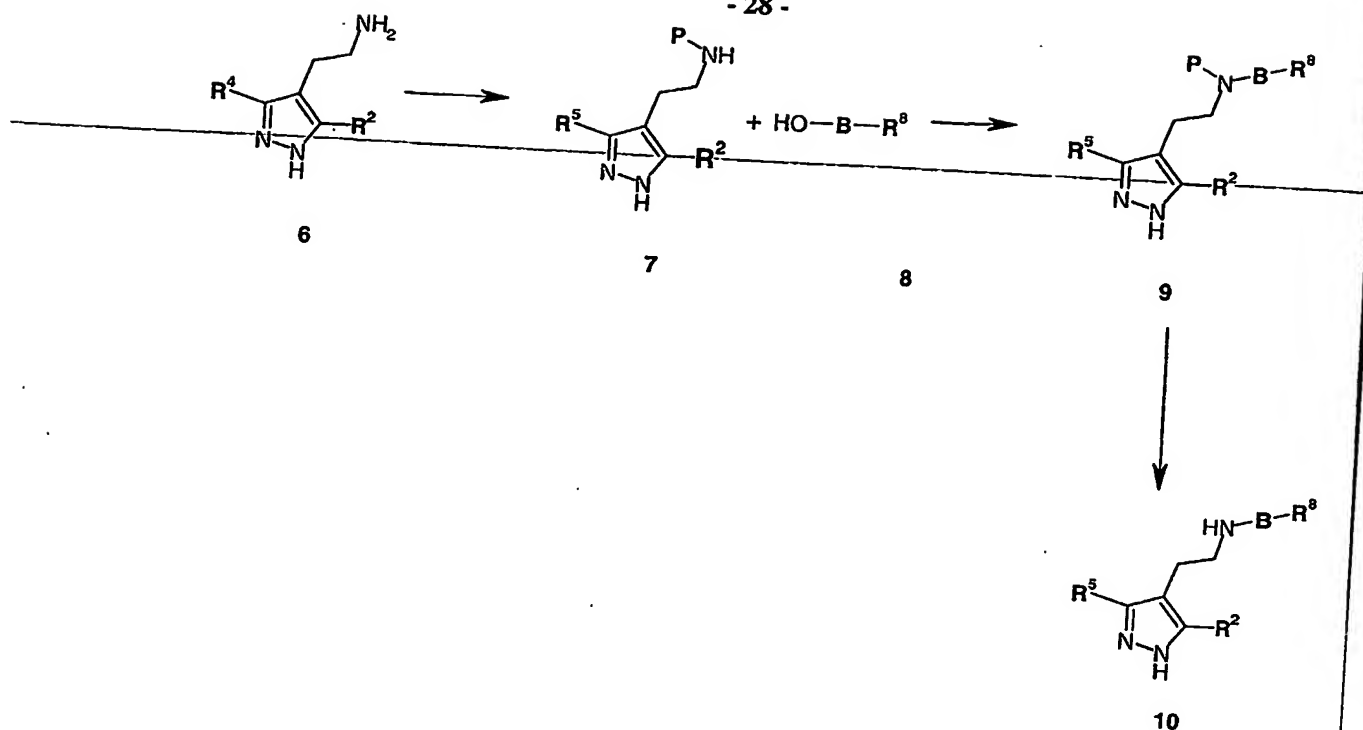
Pyrazoles, such as 3 can be synthesised in two steps (Scheme a):

- (1) by the reaction of a lactone with the appropriate ester using a Claisen condensation to form a compound of formula 2, under conditions of an inert atmosphere, such as argon, at a temperature of about 0°C in a suitable solvent such as THF.
- (2) followed by cyclization of a compound of formula 2 with hydrazine to form the pyrazole 3, at a room temperature in a suitable solvent such as ethanol.



Scheme b

The pyrazole 3 can undergo a selective alkylation reaction with a compound of formula 4, under conditions of an inert atmosphere, such as argon, in the presence of a suitable base, such as potassium carbonate in the a suitable solvent such as DMA at a temperature of about 90°C , to form a compound of formula 5.. Then the amine 6 can be prepared from a compound of formula 5 using a Mitsunobu reaction with an activating agent such as diethyldiazocarboxylate (DEAD), diisopropyldiazocarboxylate or the like with triphenylphosphine, tri-butylphosphine and the like, in an inert solvent such as benzene, toluene, tetrahydrofuran or mixtures thereof to give the (Scheme b).



Scheme c.

A suitable pyrazole 6 can be converted to a compound of formula 10 by incorporation of a suitable protecting group to form a compound of formula 7, followed by a Mitsunobu reaction with a suitable alcohol 8 to form a compound of formula 9, followed by deprotection.

EXAMPLES

The invention will now be illustrated with the following non-limiting Examples in which, unless otherwise stated:

- (i) evaporations were carried out by rotary evaporation *in vacuo* and work-up procedures were carried out after removal of residual solids such as drying agents by filtration;
- (ii) operations were carried out at room temperature, that is in the range 18-25°C and under an atmosphere of an inert gas such as argon or nitrogen;
- (iii) yields are given for illustration only and are not necessarily the maximum attainable;
- (iv) the structures of the end-products of the Formula (I) were confirmed by nuclear (generally proton) magnetic resonance (NMR) and mass spectral techniques; proton magnetic

resonance chemical shift values were measured on the delta scale and peak multiplicities are shown as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad; q, quartet, quin, quintet;

(v) intermediates were not generally fully characterised and purity was assessed by thin layer chromatography (TLC), high-performance liquid chromatography (HPLC), infra-red (IR) or NMR analysis;

(vi) chromatography was performed on silica (Merck Keisegel: Art.9385);

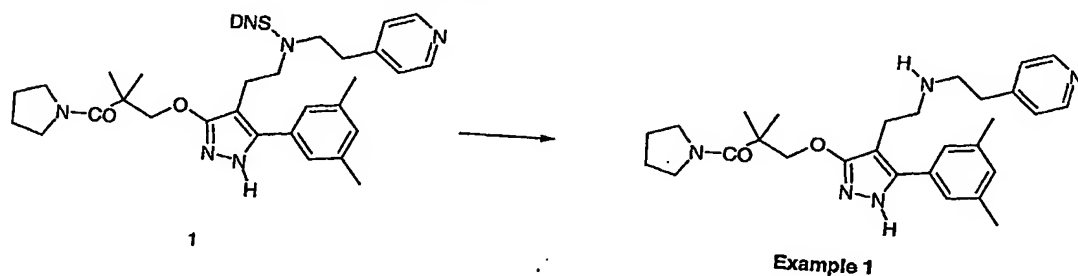
(vii) isolute™ refers to silica (SiO₂) based columns with irregular particles with an average size of 50µm with nominal 60 Å porosity [Source: Jones Chromatography, Ltd., Glamorgan, Wales, United Kingdom].

Abbreviations

DCC	1,3-dicyclohexylcarbodiimide
DEAD	diethylazodicarboxylate
15 DMAP	4-dimethylaminopyridine
DMSO	dimethyl sulphoxide
DMF	dimethylformamide
DNS	2,4-dinitrobenzenesulphonyl
EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
20	hydrochloride
HOBt	1-hydroxybenotriazole
LHMDS	lithium bis(trimethylsilyl)amide
THF	tetrahydrofuran

25 Example 1

2-[3-(2,2-dimethyl-3-oxo-3-pyrrolidin-1-ylpropoxy)-5-(3,5-dimethylphenyl)-1H-pyrazol-4-yl]-N-(2-pyridin-4-ylethyl)ethanamine



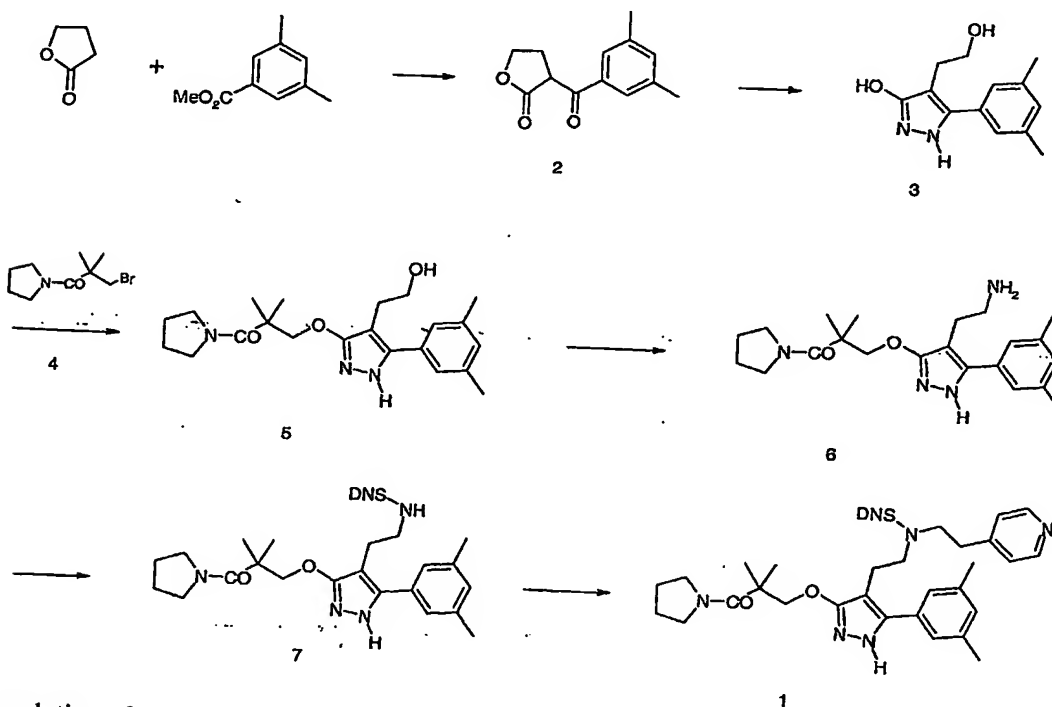
A solution of **1** (123 mg ; 0.17 mmol) in CH_2Cl_2 (3 ml) was treated dropwise with n-propylamine (140 μl ; 1.7 mmol). The mixture was stirred at room temperature for 1h and then purified directly by flash chromatography eluting with increasingly polar mixtures of
 5 EtOAc/ CH_2Cl_2 (50 to 100% EtOAc) and then MeOH/ CH_2Cl_2 (0 to 10% MeOH) to give
Example 1 as a beige solid (83 mg).

Yield : 100%

^1H NMR spectrum ($\text{DMSO } d_6$) : 1.27 (s, 6H) ; 1.75 (m, 4H) ; 2.3 (s, 6H) ; 2.55-2.95 (m, 8H) ; 3.5 (m, 4H) ; 4.18 (s, 2H) ; 7.03 (s, 1H) ; 7.10 (s, 2H) ; 7.2 (d, 2H) ; 8.44 (d, 2H).

10 MS-ESI : 490 $[\text{M}+\text{H}]^+$

The starting material was prepared as follows:-



A solution of methyl 3,5-dimethylbenzoate (25 g ; 152 mmol) and butyrolactone (40 ml ; 520 mmol) in THF (300 ml) under argon was cooled to 0°C and treated dropwise with LHMDS (200 ml ; 200 mmol ; 1M in hexanes). The mixture was stirred and allowed to warm to room temperature overnight. The THF was evaporated. The residue was taken up in Et₂O and the organic phase was washed with sat. aq. NaHCO₃, brine and dried over MgSO₄. The residue was purified by flash chromatography eluting with increasingly polar mixtures of

EtOAc/hexanes (20 to 40% EtOAc) to give an oil which slowly crystallised to give 2 as a white solid (9.2 g). During the chromatography, the starting material methyl 3,5-dimethylbenzoate (12.4g) was recovered.

5 Yield : 55% based on recovered methyl 3,5-dimethylbenzoate.

^1H NMR spectrum (CDCl_3) : 2.39 (s, 6H) ; 2.5 (m, 1H) ; 2.82 (m, 1H) ; 4.41 (m, 1H) ; 4.51 (m, 2H) ; 7.25 (s, 1H) ; 7.65 (s, 2H).

MS-ESI : 219 $[\text{M}+\text{H}]^+$

10 Compound 2 (7.43 g ; 34 mmol) was dissolved in EtOH (200 ml) and hydrazine hydrate (17.2 ml ; 354 mmol) was added. The mixture was stirred for 30 min. The solvent was evaporated and the residue was triturated with pentane to give 3 as a white solid (7.05 g).

Yield : 90%

15 ^1H NMR spectrum ($\text{DMSO } d_6$) : 2.32 (s, 6H) ; 2.58 (t, 2H) ; 3.50 (t, 2H) ; 4.8 (br s, 1H) ; 7.01 (s, 1H) ; 7.14 (s, 2H) ; 9.5 (br s, 1H).

MS-ESI : 233 $[\text{M}+\text{H}]^+$

A mixture of 3 (4.26 g ; 18.4 mmol) and 4 (4.51 g ; 19.3 mmol) in DMA (40 ml) under argon
20 was treated with K_2CO_3 (5.07 g ; 36.7 mmol). The mixture was stirred and heated at 90°C for 2h. The mixture was poured into sat. aq. NaHCO_3 , extracted with EtOAc and the organic phase was washed with water, brine and dried over MgSO_4 . The residue was purified by flash chromatography eluting with increasingly polar mixtures of EtOAc/ CH_2Cl_2 (0 to 100% EtOAc) to give the alcohol 5 as a pale yellow oil (6.56 g).

25

Yield : 93%

^1H NMR spectrum ($\text{DMSO } d_6$) : 1.30 (s, 6H) ; 1.8 (m, 4H) ; 2.33 (s, 6H) ; 2.55 (m, 2H) ; 3.32 (m, 2H) ; 3.5 (m, 4H) ; 4.17 (s, 2H) ; 4.62 (t, 1H) ; 7.04 (s, 1H) ; 7.16 (s, 2H) ; 11.9 (br s, 1H).

MS-ESI : 386 $[\text{M}+\text{H}]^+$

30

A mixture of 5 (3.85 g ; 10 mmol), phthalimide (1.62 g ; 11 mmol) and triphenylphosphine (10.5 g ; 40 mmol) in THF (100 ml) at 0°C under argon was treated with DEAD (6.33 ml ; 40 mmol). The mixture was stirred at this temperature for 1h when water was added. The mixture

was extracted with Et₂O and the organic phase was washed with water, brine and dried over MgSO₄.

Evaporation gave a crude solid which, without further purification, was immediately taken up in EtOH (50 ml) and treated with hydrazine hydrate (5 ml; 100 mmol). The mixture was stirred for 1.5h and then the EtOH was partially evaporated. Addition of CH₂Cl₂ caused precipitation of phthalhydrazide which was filtered and rinsed with CH₂Cl₂. The filtrate was evaporated and the residue was purified by flash chromatography eluting with increasingly polar mixtures of EtOAc/CH₂Cl₂ (0 to 100% EtOAc) and then MeOH/CH₂Cl₂ (0 to 8% MeOH) to give 6 as a beige solid (2.34 g).

10

Yield : 61%

¹H NMR spectrum (DMSO d₆) : 1.30 (s, 6H) ; 1.79 (m, 4H) ; 2.33 (s, 6H) ; 2.52 (m, 2H) ; 2.67 (t, 2H) ; 3.5 (m, 4H) ; 4.18 (s, 2H) ; 7.03 (s, 1H) ; 7.14 (s, 2H) ; 8.95 (br s, 1H).

MS-ESI : 385 [M+H]⁺

15

A solution of 6 (200 mg ; 0.52 mmol) in CH₂Cl₂ (5 ml) was treated with diisopropylethylamine (135 ul ; 0.78 mmol) and cooled to 0°C. A solution of 2,4-dinitrobenzenesulphonyl chloride (153 mg ; 0.57 mmol) in CH₂Cl₂ (1 ml) was added dropwise and the mixture was allowed to warm to room temperature for 30 min. The mixture was purified directly by flash chromatography eluting with increasingly polar mixtures of EtOAc/CH₂Cl₂ (0 to 50% EtOAc) to give 7 as a cream solid (224 mg).

20

Yield : 70%

¹H NMR spectrum (DMSO d₆) : 1.24 (s, 6H) ; 1.75 (m, 4H) ; 2.29 (s, 6H) ; 2.57 (m, 2H) ; 3.11 (m, 2H) ; 3.5 (m, 4H) ; 4.15 (s, 2H) ; 7.0 (s, 1H) ; 7.03 (s, 2H) ; 8.14 (d, 1H) ; 8.56 (q, 1H) ; 8.6 (br s, 1H) ; 8.83 (d, 1H).

25

MS-ESI : 615 [M+H]⁺

A mixture of 7 (170 mg ; 0.27 mmol), 4-(2-hydroxyethyl)-pyridine (38 mg ; 0.3 mmol) and triphenylphosphine (283 mg ; 1.08 mmol) in THF (10 ml) at 0°C under argon was treated with DEAD (170 ul ; 1.08 mmol). The mixture was allowed to warm to room temperature for 30 min. when water was added. The mixture was extracted with EtOAc and the organic phase was washed with water, brine and dried over MgSO₄. The residue was purified by flash

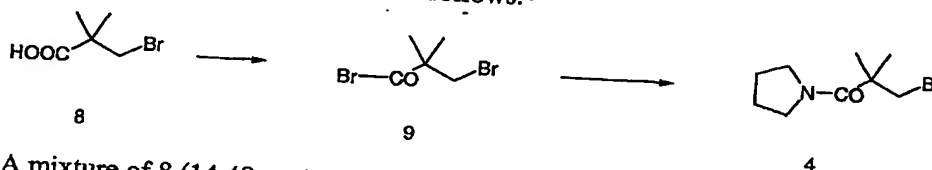
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chromatography eluting with increasingly polar mixtures of EtOAc/CH₂Cl₂ (0 to 100% EtOAc) 1 as a white solid (123 mg).

Yield : 63%

¹H NMR spectrum (DMSO d₆) : 1.27 (s, 6H) ; 1.7 (m, 4H) ; 2.28 (s, 6H) ; 2.69 (t, 2H) ; 2.83 (t, 2H) ; 3.4 (m, 4H) ; 3.48 (t, 2H) ; 3.56 (t, 2H) ; 4.21 (s, 2H) ; 7.01 (s, 1H) ; 7.08 (s, 2H) ; 7.19 (d, 2H) ; 8.15 (d, 1H) ; 8.41 (d, 2H) ; 8.42 (q, 1H) ; 8.89 (d, 1H).
MS-ESI : 720 [M+H]⁺

10 Starting material 4 was prepared as follows:-



A mixture of 8 (14.48 g ; 80 mmol) and oxalyl bromide (43.2 g ; 200 mmol) containing one drop of DMF was heated at 50°C for 2h and then cooled. The excess of oxalyl bromide was evaporated and the residue azeotroped with toluene to give crude 9 which was taken up directly in CH₂Cl₂ (25 ml) and cooled to 0°C. Diisopropylethylamine (14 ml ; 80 mmol) was added followed by a solution of pyrrolidine (3.3 ml ; 40 mmol) in CH₂Cl₂ (30 ml). The mixture was allowed to warm to room temperature overnight and was diluted with CH₂Cl₂, washed with aq. HCl (2N), aq. NaOH (1N), water, brine and dried over MgSO₄. The residue was purified by flash chromatography eluting with increasingly polar mixtures of EtOAc/CH₂Cl₂ (5 to 10% EtOAc) to give 4 as a white solid (6.5 g).

Yield : 70%

¹H NMR spectrum (DMSO d₆) : 1.39 (s, 6H) ; 1.9 (m, 4H) ; 3.57 (m, 4H) ; 3.62 (s, 2H)
MS-ESI : 235 [M+H]⁺

THERAPEUTIC USES

Compounds of Formula (I) are provided as medicaments for antagonising gonadotropin releasing hormone (GnRH) activity in a patient, eg, in men and/or women. To this end, a compound of Formula (I) can be provided as part of a pharmaceutical formulation which also includes a pharmaceutically acceptable diluent or carrier (eg, water). The formulation may be in the form of tablets, capsules, granules, powders, syrups, emulsions (eg,

lipid emulsions), suppositories, ointments, creams, drops, suspensions (eg, aqueous or oily suspensions) or solutions (eg, aqueous or oily solutions). If desired, the formulation may include one or more additional substances independently selected from stabilising agents, wetting agents, emulsifying agents, buffers, lactose, sialic acid, magnesium stearate, terra
5 alba, sucrose, corn starch, talc, gelatin, agar, pectin, peanut oil, olive oil, cacao butter and ethylene glycol.

The compound is preferably orally administered to a patient, but other routes of administration are possible, such as parenteral or rectal administration. For intravenous, subcutaneous or intramuscular administration, the patient may receive a daily dose of
10 0.1mgkg^{-1} to 30mgkg^{-1} (preferably, 5mgkg^{-1} to 20mgkg^{-1}) of the compound, the compound being administered 1 to 4 times per day. The intravenous, subcutaneous and intramuscular dose may be given by means of a bolus injection. Alternatively, the intravenous dose may be given by continuous infusion over a period of time. Alternatively, the patient may receive a daily oral dose which is approximately equivalent to the daily parenteral dose, the
15 composition being administered 1 to 4 times per day. A suitable pharmaceutical formulation is one suitable for oral administration in unit dosage form, for example as a tablet or capsule, which contains between 10mg and 1g (preferably, 100 mg and 1g) of the compound of the invention.

Buffers, pharmaceutically acceptable co-solvents (eg, polyethylene glycol, propylene
20 glycol, glycerol or EtOH) or complexing agents such as hydroxy-propyl β cyclodextrin may be used to aid formulation.

One aspect of the invention relates to the use of compounds according to the invention for reducing the secretion of LH and/or FSH by the pituitary gland of a patient. In this respect, the reduction may be by way of a reduction in biosynthesis of the LH and FSH and/or
25 a reduction in the release of LH and FSH by the pituitary gland. Thus, compounds according to the invention can be used for therapeutically treating and/or preventing a sex hormone related condition in the patient. By "preventing" we mean reducing the patient's risk of contracting the condition. By "treating" we mean eradicating the condition or reducing its severity in the patient. Examples of sex hormone related conditions are: a sex hormone
30 dependent cancer, benign prostatic hypertrophy, myoma of the uterus, endometriosis, polycystic ovarian disease, uterine fibroids, prostatic cancer, myoma uteri, hirsutism and precocious puberty. Examples of sex hormone dependent cancers are: prostatic cancer, uterine cancer, breast cancer and pituitary gonadotrope adenoma.

The compounds of the invention may be used in combination with other drugs and therapies used to treat / prevent sex-hormone related conditions.

If formulated as a fixed dose such combination products employ the compounds of this invention within the dosage range described herein and the other pharmaceutically-active agent within its approved dosage range. Sequential use is contemplated when a combination formulation is inappropriate.

In the field of medical oncology examples of such combinations include combinations with the following categories of therapeutic agent:

- i) anti-angiogenic agents (for example linomide, inhibitors of integrin $\alpha v \beta 3$ function, angiostatin, endostatin, razoxin, thalidomide) and including vascular endothelial growth factor (VEGF) receptor tyrosine kinase inhibitors (RTKIs) (for example those described in international patent applications publication nos. WO-97/22596, WO-97/30035, WO-97/32856 and WO-98/13354, the entire disclosure of which documents is incorporated herein by reference);
- 15 ii) cytostatic agents such as anti-oestrogens (for example tamoxifen, toremifene, raloxifene, droloxifene, idoxifene), progestogens (for example megestrol acetate), aromatase inhibitors (for example anastrozole, letrozole, vorazole, exemestane), anti-progestogens, anti-androgens (for example flutamide, nilutamide, bicalutamide, cyproterone acetate), inhibitors of testosterone 5α -dihydroreductase (for example finasteride), anti-20 invasion agents (for example metalloproteinase inhibitors like marimastat and inhibitors of urokinase plasminogen activator receptor function) and inhibitors of growth factor function, (such growth factors include for example epidermal growth factor (EGF), platelet derived growth factor and hepatocyte growth factor such inhibitors include growth factor antibodies, growth factor receptor antibodies, tyrosine kinase inhibitors and serine/threonine kinase 25 inhibitors);
- iii) biological response modifiers (for example interferon);
- iv) antibodies (for example edrecolomab); and
- v) anti-proliferative/anti-neoplastic drugs and combinations thereof, as used in medical oncology, such as anti-metabolites (for example anti-folates like methotrexate, 30 fluoropyrimidines like 5-fluorouracil, purine and adenosine analogues, cytosine arabinoside); anti-tumour antibiotics (for example anthracyclines like doxorubicin, daunomycin, epirubicin and idarubicin, mitomycin-C, dactinomycin, mithramycin); platinum derivatives (for example cisplatin, carboplatin); alkylating agents (for example nitrogen mustard, melphalan,

chlorambucil, busulphan, cyclophosphamide, ifosfamide, nitrosoureas, thiotepa); anti-mitotic agents (for example vinca alkaloids like vincristine and taxoids like taxol, taxotere); enzymes (for example asparaginase); thymidylate synthase inhibitors (for example raltitrexed); topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, 5 amsacrine, topotecan, irinotecan).

The compounds of the invention may also be used in combination with surgery or radiotherapy.

ASSAYS

- 10 The ability of compounds according to the invention to act as antagonists of GnRH can be determined using the following in vitro assays.

Binding Assay Using Rat pituitary GnRH Receptor

The assay is performed as follows:-

1. Incubate crude plasma membranes prepared from rat pituitary tissues in a Tris.HCl buffer (pH. 7.5, 50 mM) containing bovine serum albumin (0.1%), [I-125]D-t-Bu-Ser6-Pro9-ethyl amide-GnRH, and the test compound. Incubation is at 4°C for 90 minutes to 2 hours.
 2. Rapidly filter and repeatedly wash through a glass fibre filter.
 3. Determine the radioactivity of membrane bound radio-ligands using a gamma counter.
- 20 From this data, the IC₅₀ of the test compound can be determined as the concentration of the compound required to inhibit radio-ligand binding to GnRH receptors by 50%. Compounds according to the present invention have activity at a concentration from 1nM to 5 µM.

25 Binding Assay Using Human GnRH Receptor

Crude membranes prepared from CHO cells expressing human GnRH receptors are sources for the GnRH receptor. The binding activity of compounds according to the invention can be determined as an IC₅₀ which is the compound concentration required to inhibit the specific binding of [¹²⁵I]buserelin to GnRH receptors by 50%. [¹²⁵I]Buserelin (a peptide 30 GnRH analogue) is used here as a radiolabelled ligand of the receptor.

Assay to Determine Inhibition of LH release

The LH release assay can be used to demonstrate antagonist activity of compounds, as demonstrated by a reduction in GnRH-induced LH release.

Preparation of Pituitary Glands

- 5 Pituitary glands obtained from rats are prepared as follows. Suitable rats are Wistar male rats (150-200g) which have been maintained at a constant temperature (eg, 25°C) on a 12 hour light/12 hour dark cycle. The rats are sacrificed by decapitation before the pituitary glands are aseptically removed to tube containing Hank's Balanced Salt Solution (HBSS). The glands are further processed by:-
- 10
1. Centrifugation at 250 x g for 5 minutes;
 2. Aspiration of the HBSS solution;
 3. Transfer of the glands to a petri dish before mincing with a scalpel;
 4. Transfer of the minced tissue to a centrifuge tube by suspending the tissue three
 - 15 successive times in 10 ml aliquots of HBSS containing 0.2% collagenase and 0.2% hyaluronidase;
 5. Cell dispersion by gentle stirring of the tissue suspension while the tube is kept in a water bath at 37°C;
 6. Aspiration 20 to 30 times using a pipette, undigested pituitary fragments being allowed to
 - 20 settle for 3 to 5 minutes;
 7. Aspiration of the suspended cells followed by centrifugation at 1200 x g for 5 minutes;
 8. Re-suspension of the cells in culture medium of DMEM containing 0.37% NaHCO₃, 10% horse serum, 2.5% foetal bovine serum, 1% non essential amino acids, 1% glutamine and 0.1% gentamycin;
 - 25 9. Treatment of the undigested pituitary fragments 3 times with 30 ml aliquots of the collagenase and hyaluronidase;
 10. Pooling of the cell suspensions and dilution to a concentration of 3×10^5 cells/ml;
 11. Placing of 1.0ml of this suspension in each of a 24 well tray, with the cells being maintained in a humidified 5% CO₂/95% air atmosphere at 37°C for 3 to 4 days.
- 30

Testing of Compounds

The test compound is dissolved in DMSO to a final concentration of 0.5% in the incubation medium.

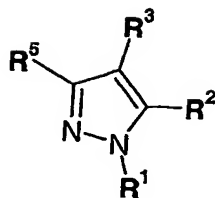
1.5 hours prior to the assay, the cells are washed three times with DMEM containing 0.37% NaHCO_3 , 10% horse serum, 2.5% foetal bovine serum, 1% non essential amino acids (100X), 1% glutamine (100X), 1% penicillin/streptomycin (10,000 units of each per ml) and 25 mM HEPES at pH 7.4. Immediately prior to the assay, the cells are again washed twice in this medium.

Following this, 1ml of fresh medium containing the test compound and 2nM GnRH is added to two wells. For other test compounds (where it is desired to test more than one compound), these are added to other respective duplicate wells. Incubation is then carried out at 37°C for three hours.

Following incubation, each well is analysed by removing the medium from the well and centrifuging the medium at 2000 x g for 15 minutes to remove any cellular material. The supernatant is removed and assayed for LH content using a double antibody radio-immuno assay. Comparison with a suitable control (no test compound) is used to determine whether the test compound reduces LH release. Compounds according to the present invention have activity at a concentration from 1nM to 5 μM .

CLAIMS:

1. A compound of Formula (I),



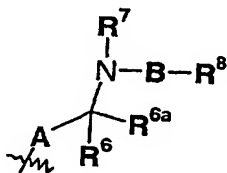
Formula (I)

wherein

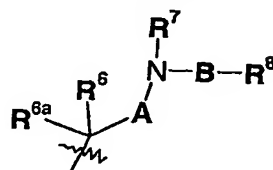
R^1 is selected from: hydrogen, optionally-substituted C_{1-6} alkyl, optionally substituted aryl or optionally-substituted aryl C_{1-6} alkyl;

R^2 is an optionally-substituted mono or bi-cyclic aromatic ring;

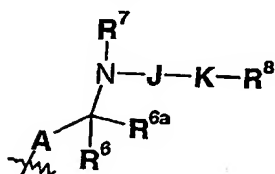
R^3 is selected from a group of Formula (IIa) to Formula (IIf):



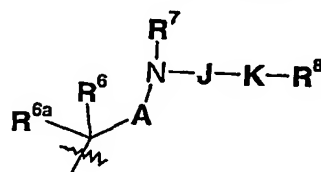
Formula (IIa)



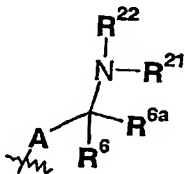
Formula (IIb)



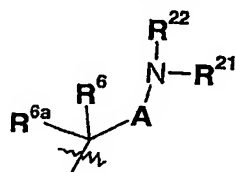
Formula (IIc)



Formula (IId)



Formula (IIe)



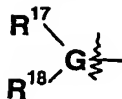
Formula (IIIf)

R^4 is selected from: hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted aryl, C_{1-3} perfluoroalkyl, cyano, nitro, halo, $R^9O(CH_2)_m$ -, $R^9C(O)N(R^{10})$ -,

$R^9R^{10}NC(O)N(R^{10})$ - or $R^9S(O)_n$ -;

R^5 is a group of Formula (III):

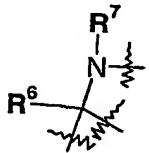
- 40 -



Formula (III)

R^6 and R^{6a} are independently selected from hydrogen, optionally substituted C_{1-6} alkyl, optionally-substituted aryl or optionally substituted aryl C_{1-6} alkyl, or R^6 and R^{6a} taken together and the carbon atom to which they are attached form a carbocyclic ring of 3-7 atoms, or R^6 and R^{6a} taken together and the carbon atom to which they are attached form a carbonyl group;

or when A is not a direct bond the group forms a carbocyclic ring of 3-7 carbon atoms or a heterocyclic ring containing one or more heteroatoms;



or the group forms a heterocyclic ring containing 3-7 carbon atoms and one or more heteroatoms;

R^7 is selected from: hydrogen, optionally-substituted C_{1-6} alkyl, optionally-substituted aryl C_{1-6} alkyl, optionally-substituted aryl, optionally substituted heterocyclyl, optionally substituted heterocyclyl C_{1-6} alkyl, R^9OC_{1-6} alkyl-, $R^9R^{10}NC_{1-6}$ alkyl-, $R^9R^{10}NC(O)C_{1-6}$ alkyl, $-C(NR^9R^{10})=NH$;

or when R^3 is a group of Formula (Iic) or (IId) R^7 is of the formula $-J-K-R^8$;

R^8 is selected from:

- (i) hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo C_{1-6} alkyl, C_{1-4} alkoxy C_{1-4} alkyl, hydroxy, hydroxy C_{1-6} alkyl, cyano, N- C_{1-4} alkylamino, N,N-di- C_{1-4} alkylamino, C_{1-6} alkyl- $S(O_n)-$, $-O-R^b$, $-NR^bR^c$, $-C(O)-R^b$, $-C(O)O-R^b$, $-CONR^bR^c$ or $NH-C(O)-R^b$,

where R^b and R^c are independently selected from hydrogen and C_{1-4} alkyl optionally substituted with hydroxy, amino, N- C_{1-4} alkylamino, N,N-di- C_{1-4} alkylamino, $HO-C_{2-4}$ alkyl-NH- or $HO-C_{2-4}$ alkyl-N(C_{1-4} alkyl)-;

- (ii) nitro when B is a group of Formula (IV) and X is CH and p is 0;

- (iii) C_{3-7} cycloalkyl, aryl or aryl C_{1-6} alkyl each of which is optionally substituted by R^{12} , R^{13} and R^{14} .

(iv) $-(Q)-\text{aryl}$, $-(Q)-\text{heterocyclyl}$, $-\text{aryl}-(Q)-\text{aryl}$, each of which is optionally substituted by R^{12} , R^{13} and R^{14}

wherein $-(Q)-$ is selected from E, F or a direct bond;

(v) heterocyclyl or heterocyclyl C_{1-6} alkyl each of which is optionally substituted by R^{12} , R^{13} and R^{14} ;

(vi) a group selected from R^{12} , R^{13} and R^{14} ;

R^9 and R^{10} are independently selected from: hydrogen, hydroxy, optionally substituted C_{1-6} alkyl, optionally substituted aryl, optionally substituted aryl C_{1-6} alkyl, an optionally substituted carbocyclic ring of 3-7 atoms, optionally substituted heterocyclyl, optionally substituted heterocyclyl C_{1-6} alkyl or R^9 and R^{10} taken together can form an optionally substituted ring of 3-9 atoms or R^9 and R^{10} taken together with the carbon atom to which they are attached form a carbonyl group;

R^{11} is selected from: hydrogen, optionally substituted C_{1-6} alkyl, or $N(R^9R^{10})$;

R^{12} is selected from: hydrogen, hydroxy, $R^{17}R^{18}N-$, optionally substituted C_{1-6} alkyl- $SO_2N(R^9)-$, optionally substituted aryl- $SO_2N(R^9)-$, C_{1-3} perfluoroalkyl- $SO_2N(R^9)-$; optionally substituted C_{1-6} alkyl- $N(R^9)SO_2-$, optionally substituted aryl- $N(R^9)SO_2-$, C_{1-3} perfluoroalkyl- $N(R^9)SO_2-$ optionally substituted C_{1-6} alkanoyl- $N(R^9)SO_2-$; optionally substituted aryl- $C(O)N(R^9)SO_2-$, optionally substituted C_{1-6} alkyl- $S(O_n)-$, optionally substituted aryl- $S(O_n)-$, C_{1-3} perfluoroalkyl-, C_{1-3} perfluoroalkoxy, optionally substituted C_{1-6} alkoxy, carboxy, halo, nitro or cyano;

R^{13} and R^{14} are independently selected from: hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, cyano, nitro, C_{1-3} perfluoroalkyl-, C_{1-3} perfluoroalkoxy, optionally substituted aryl, optionally substituted aryl C_{1-6} alkyl, $R^9O(CH_2)_s-$, $R^9(O)O(CH_2)_s-$, $R^9OC(O)(CH_2)_s-$, $R^{16}S(O_n)(CH_2)_s-$, $R^9R^{10}NC(O)(CH_2)_s-$ or halo;

R^{15} is selected from: hydrogen, optionally substituted C_{1-6} alkyl, $R^{19}OC(O)-$, $R^9R^{10}NC(O)-$, $R^9C(O)-$, $R^9S(O_n)-$;

R^{16} is selected from: hydrogen, C_{1-6} alkyl, C_{1-3} perfluoroalkyl or optionally-substituted aryl;

R^{17} is independently selected from: hydrogen, hydroxy, cyano or optionally substituted C_{1-6} alkyl;

R^{18} is a group of formula $R^{18a}-C(R^9R^{10})_{0-1}$ wherein R^{18a} is selected from:

$R^{19}OC(O)-$, $R^9R^{10}NC(O)-$, $R^9R^{10}N-$, $R^9C(O)-$, $R^9C(O)N(R^{10})-$, $R^9R^{10}NC(O)-$,
 $R^9R^{10}NC(O)N(R^{10})-$, $R^9SO_2N(R^{10})-$, $R^9R^{10}NSO_2N(R^{10})-$, $R^9C(O)O-$, $R^9OC(O)-$,
 $R^9R^{10}NC(O)O-$, R^9O- , $R^9S(O_n)-$, $R^9R^{10}NS(O_n)-$, optionally substituted C_{1-6} alkyl,

optionally substituted heterocyclyl;

or R^{17} and R^{18} when taken together form an optionally substituted carbocyclic ring of 3-7 atoms or optionally substituted heterocyclyl;

R^{19} is selected from: hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted aryl, optionally substituted aryl C_{1-6} alkyl, optionally substituted C_{3-7} cycloalkyl, optionally substituted heterocyclyl or optionally substituted heterocyclyl C_{1-6} alkyl;

R^{20} is selected from R^{12} or R^{13} ;

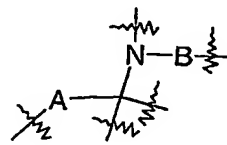
R^{21} and R^{22} are independently selected from hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-7} cycloalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclyl C_{1-6} alkyl, optionally substituted C_{3-6} alkenyl, optionally substituted C_{3-6} alkynyl, $-(C_{1-5}alkyl)_{aa}-S(O_n)-(C_{1-5}alkyl)_{bb}-$; $R^9R^{10}NC_{2-6}alkyl$, $R^9OC_{2-6}alkyl$ or $R^9R^{10}NC(O)C_{2-6}alkyl$, with the proviso that R^9 and R^{10} independently or taken together are not optionally substituted aryl or optionally substituted aryl C_{1-6} alkyl; or

R^{21} and R^{22} taken together form an optionally substituted non-aromatic heterocyclic ring;

A is selected from:

- (i) a direct bond;
- (ii) optionally-substituted C_{1-5} alkylene wherein the optional substituents are independently selected from: optionally-substituted C_{1-6} alkyl, optionally-substituted aryl, optionally substituted aryl C_{1-6} alkyl or substituted aryl C_{1-6} alkyl;
- (iii) a carbocyclic ring of 3-7 atoms;
- (iv) a carbonyl group;

or when R^3 is a group of Formula (IIa) or (IIb), the group



forms

a heterocyclic ring containing 3-7 carbon atoms and one or more heteroatoms;

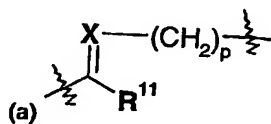
or when R^3 is a group of Formula (IIa), (IIb), (IIc) or (IId), the group



forms a heterocyclic ring containing 3-7 carbon atoms and one or more heteroatoms;

B is selected from:

- (i) a direct bond;
- (ii) a group of Formula (IV)



Formula (IV)

wherein:

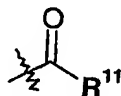
X is selected from N or CH,

wherein at position (a) Formula (IV) is attached to the nitrogen atom and the $(CH_2)_p$ group is attached to R^8 ; and

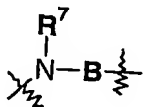
- (iii) a group independently selected from: optionally substituted C_{1-6} alkylene, optionally substituted C_{3-7} cycloalkyl, optionally substituted C_{3-6} alkenylene, optionally substituted C_{3-6} alkynyl, C_{1-6} alkoxy, $(C_{1-5}alkyl)_{aa}-S(O_n)-(C_{1-5}alkyl)_{bb}$, $(C_{1-5}alkyl)_{aa}-O-(C_{1-5}alkyl)_{bb}$ or $(C_{1-5}alkyl)_{aa}-N(R^{15})-(C_{1-5}alkyl)_{bb}$,

wherein R^{15} and the $(C_{1-5}alkyl)_{aa}$ or $(C_{1-5}alkyl)_{bb}$ chain can be joined to form a ring;

or the group $-B-R^8$ represents a group of Formula (V)

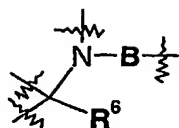


Formula (V);



or the group
atoms;

together forms a heterocyclic ring containing 5-7 carbons



or the group forms a heterocyclic ring containing 3-7 carbon atoms

and one or more heteroatoms;

E is $-\text{O}-$, $-\text{S}(\text{O}_n)$, $-\text{C}(\text{O})-$, $-\text{NR}^{15}$ or $-\text{C}(\text{R}^9\text{R}^{10})_q$;

F is $-\text{E}(\text{CH}_2)_r-$;

5 G is selected from: hydrogen, halo, N, O, $\text{S}(\text{O}_n)$, $\text{C}(\text{O})$, $\text{C}(\text{R}^9\text{R}^{10})_t$, optionally substituted C_{2-6} alkenylene, optionally substituted C_{2-6} alkynylene or a direct bond to R^{18} ,

J is a group of the formula: $-(\text{CH}_2)_s-\text{L}-(\text{CH}_2)_s-$ wherein when s is greater than 0, the alkylene group is optionally substituted

10 K is selected from: a direct bond, $-\text{O}-(\text{CH}_2)_s-$, $-\text{C}(\text{O})-(\text{CH}_2)_s-$, $-\text{S}(\text{O}_n)-(\text{CH}_2)_s-$, $-\text{N}(\text{R}^{18})-(\text{CH}_2)_s-$, $-\text{OC}(\text{O})-(\text{CH}_2)_s-$, $-\text{C}(\text{O})\text{O}-(\text{CH}_2)_s-$, $-\text{OS}(\text{O}_n)-(\text{CH}_2)_s-$, or $-\text{S}(\text{O}_n)-\text{O}-(\text{CH}_2)_s-$;

L is selected from optionally substituted aryl or optionally substituted heterocyclyl;

M is $-(\text{CH}_2)_{0-2}-\text{O}-$;

15 n is an integer between 0 and 2;

p is an integer between 0 and 4;

q is an integer between 0 and 4;

r is an integer between 0 and 4;

s is an integer between 0 and 4; and

20 t is an integer between 0 and 4;

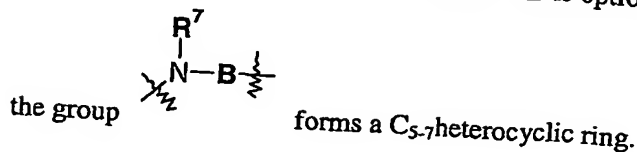
with the proviso that

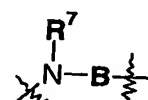
(i) when G is hydrogen or halo, then R^{17} and R^{18} are both absent;

(ii) when G is O, $\text{S}(\text{O}_n)$, $\text{C}(\text{O})$ or $\text{C}(\text{R}^{11}\text{R}^{12})_t$ then G is substituted by a single group independently selected from the definition of R^{17} or R^{18} and when G is a direct bond to R^{18} then G is substituted by a single group selected from R^{18} ; and
25 or a salt, pro-drug or solvate thereof.

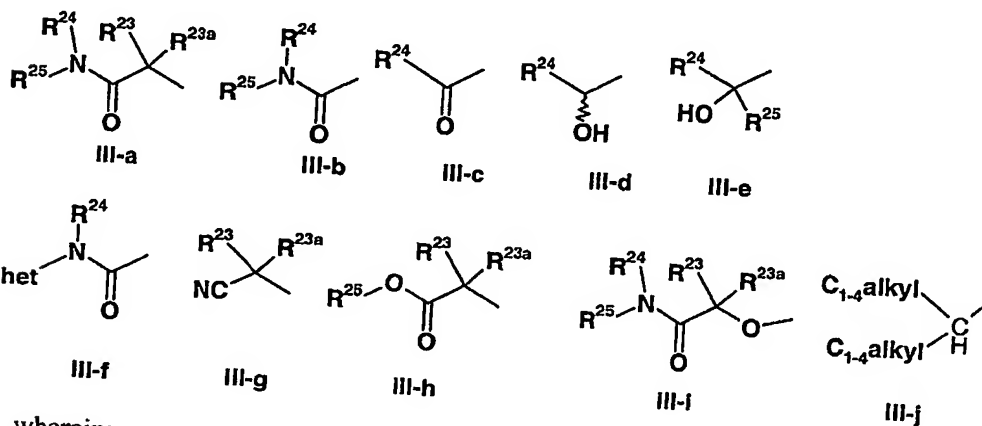
2. A compound according to Claim 1 wherein R^3 is selected from a group of Formula (IIa) or Formula (IIb).

3. A compound according to Claim 2 wherein B is optionally substituted C₁₋₆alkylene or



4. A compound according to Claim 3 wherein the group  forms piperazinyl.

5. A compound according to any one of Claims 2, 3, 4 or 5 wherein R⁸ is selected from C₃₋₇cycloalkyl, aryl, arylC₁₋₆alkyl heterocyclyl or heterocyclylC₁₋₆alkyl each of which is optionally substituted by R¹², R¹³ and R¹⁴.
6. A compound according to Claim 5 wherein R⁸ is selected from: pyridyl, thiazolyl, pyrrolidinyl, phenyl and benzyl.
7. A compound according to any one of the preceding claims wherein R⁵ is a group of Formula (III) wherein the group of Formula (III) is selected from any one of III-a to III-j;



wherein:

het represents an optionally substituted 3- to 8- membered heterocyclic ring containing from 1 to 4 heteroatoms independently selected from O, N and S;

R^{23} and R^{23a} are independently selected from hydrogen or optionally substituted C_{1-8} alkyl; or R^{23} and R^{23a} together with the carbon to which they are attached form an optionally substituted 3 to 7-membered cycloalkyl ring

R^{24} is selected from hydrogen, optionally substituted C_{1-8} alkyl, optionally substituted aryl, $-R^d-Ar$, where R^d represents C_{1-8} alkylene and Ar represents optionally substituted aryl, and optionally substituted 3- to 8- membered heterocyclic ring optionally containing from 1 to 3 further heteroatoms independently selected from O, N and S;

R^{25} is selected from hydrogen; optionally substituted C_{1-8} alkyl and optionally substituted aryl;

or where the group of Formula (III) represents a group of Formula III-a, III-b or III-i, then the group $NR^{24}(-R^{25})$ represents an optionally substituted 3- to 8-membered heterocyclic ring optionally containing from 1 to 3 further heteroatoms independently selected from O, N and S;

or where the group of Formula (III) represents structure III-e, R^{24} and R^{25} together with the carbon to which they are attached represents an optionally substituted 3- to 8- membered heterocyclic ring optionally containing from 1 to 4 heteroatoms independently selected from O, N and S;

8. A compound according to any one of the preceding claims wherein R^2 is selected from an optionally substituted monocyclic aromatic ring structure wherein the optional substituents are selected from cyano, NR^eR^f , optionally substituted C_{1-8} alkyl, optionally substituted C_{1-8} alkoxy or halo wherein R^e and R^f are independently selected from hydrogen, C_{1-6} alkyl or aryl.

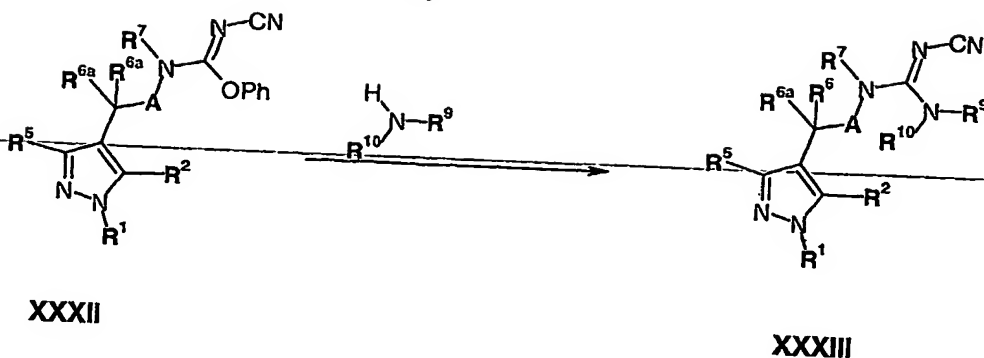
9. A compound according to any one of the preceding claims wherein R^1 is hydrogen.

10. A compound selected from:

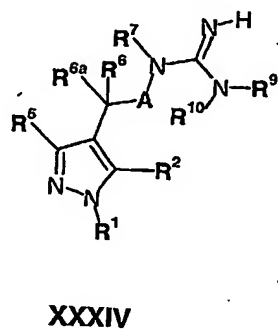
2-[3-(2,2-dimethyl-3-oxo-3-pyrrolidin-1-ylpropoxy)-5-(3,5-dimethylphenyl)-1H-pyrazol-4-yl]-N-(2-pyridin-4-ylethyl)ethanamine;

2-[3-(2,2-dimethyl-3-oxo-3-pyrrolidin-1-ylpropoxy)-5-(3,5-dimethylphenyl)-1H-pyrazol-4-yl]-N-(2-pyridin-4-ylbutyl)ethanamine;

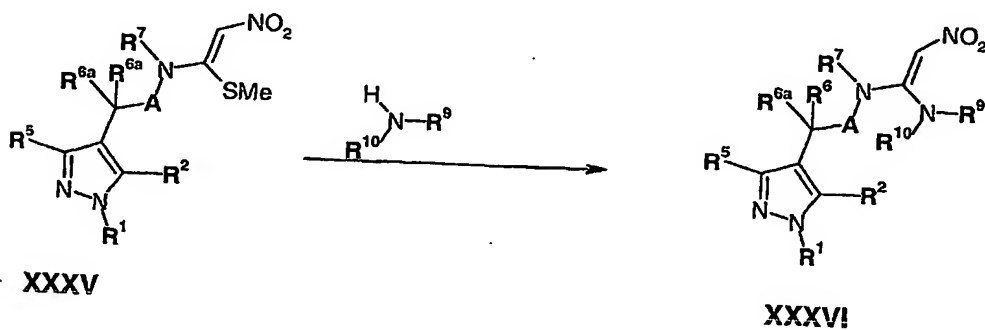
- 2-[3-(2,2-dimethyl-3-oxo-3-(7-azabicyclo[2.2.1]hept-7-yl)propoxy)-5-(3,5-dimethylphenyl)-1*H*-pyrazol-4-yl]-*N*-(2-pyridin-4-ylethyl)ethanamine; and
2-[3-(2,2-dimethyl-3-oxo-3-(7-azabicyclo[2.2.1]hept-7-yl)propoxy)-5-(3,5-dimethylphenyl)-1*H*-pyrazol-4-yl]-*N*-(2-pyridin-4-ylbutyl)ethanamine;
5 or a salt, pro-drug or solvate thereof.
11. A compound, or salt, pro-drug or solvate thereof, according to any one of Claims 1 to 10 for use as a medicament.
- 10 12. A pharmaceutical formulation comprising a compound, or salt, pro-drug or solvate thereof, according to any one of Claims 1 to 10 and a pharmaceutically acceptable diluent or carrier.
13. Use of a compound, or salt, pro-drug or solvate thereof, according to any one of Claims 1 to 10, in the manufacture of a medicament for antagonising gonadotropin releasing hormone activity.
15
14. Use of a compound, or salt, pro-drug or solvate thereof, according to any one of Claims 1 to 10, in the manufacture of a medicament for administration to a patient, for therapeutically treating and/or preventing a sex hormone related condition in the patient.
20
15. The use according to claim 14, wherein the sex hormone related condition is selected from a sex hormone dependent cancer, benign prostatic hypertrophy or myoma of the uterus.
25
16. A process of producing a compound or Formula (I) wherein R^3 is a group of Formula (IIb) and B is a group of Formula (V), or salt, pro-drug or solvate thereof, according to any one of Claims 1 to 10, wherein the process comprises a reaction step selected from any one of steps (a) to (f):-
30 (a) for compounds wherein X is N and R^8 is CN, reaction of a compound of formula XXXII as follows



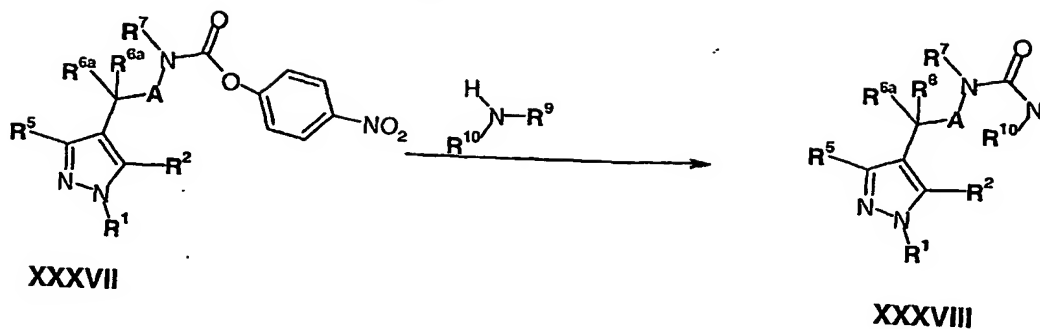
- 5 (b) for compounds wherein X is N and R^8 is hydrogen, cleavage of the cyano group of compound of formula XXXIII in the presence of acid to produce compound of formula XXXIV



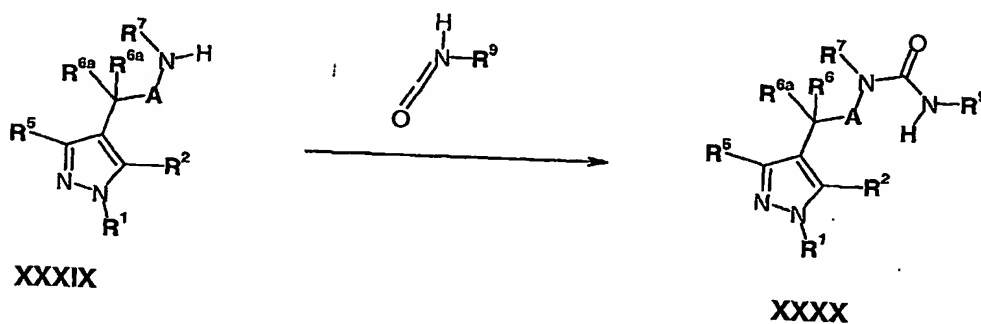
- (c) for compounds wherein X is CH and R^8 is NO_2 , reaction of compound of formula XXXV as follows



- 10 (d) for compounds where $X-R^8$ is O, reaction of compound of formula XXXVII as follows

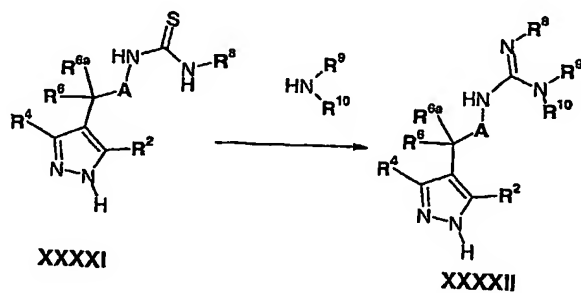


- (e) for compounds where $X-R^8$ is O, reaction of compound of formula XXXIX as follows



5

- (f) to form a compound wherein X is nitrogen reaction of a compound of formula XXXXI as follows



10

and thereafter if necessary:

- i) converting a compound of the Formula (I) into another compound of the Formula (I);
- ii) removing any protecting groups;
- iii) forming a salt, pro-drug or solvate.

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